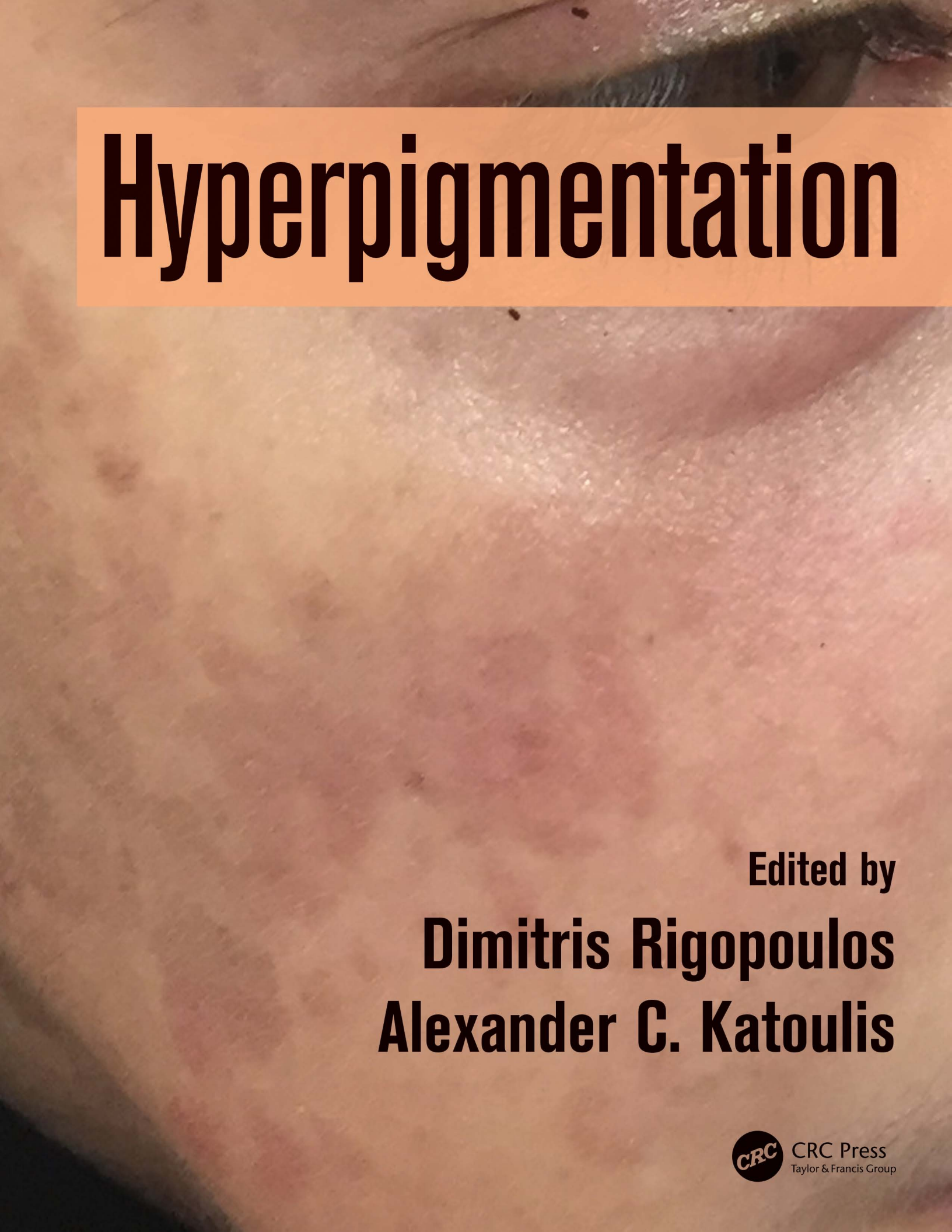


A close-up photograph of human skin showing various types of hyperpigmentation, including brown spots, blotches, and a larger, faint, irregularly shaped area of discoloration. The skin tone is light to medium.

Hyperpigmentation

Edited by
Dimitris Rigopoulos
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Hyperpigmentation



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Histology, Physiology, and Pathophysiology of Skin Pigmentation

INTRODUCTION

Skin, the finest covering of the body, functions as an active biological barrier separating the internal homeostasis from the environment outside. Skin protects our internal organs and system from harsh environments by functioning as a barrier to microbes, chemicals, and ultraviolet radiation (UVR) found in sunlight and also prevents water loss. As one of the most conspicuous human polytypic variations, skin color has probably attracted more scholarly attention than any other aspect of human variability. The color of the skin plays a major role in the appearance of an individual, as *beauty is nothing but skin deep*.¹

BIOLOGY OF SKIN COLOR

Two types of melanin pigmentation occur in humans.² The first is constitutive skin color, which is the amount of melanin pigmentation that is genetically determined in the absence of sun exposure and other influences. The other is facultative (inducible) skin color, or “tan,” which results from sun exposure.

Human skin color is determined by the total quantity of melanin, the proportion between the brown-black eumelanin and the yellow-red pheomelanin, and its distribution through the epidermis.^{3,4} In addition to melanin (brown), the blood flow (red oxygenated hemoglobin and blue reduced hemoglobin) and β -carotene (yellow) content of skin also contribute to skin color.

The major determinant of normal skin color is the activity of melanocytes, i.e., the quantity and quality of pigment production, not the density of melanocytes. The melanocyte is a neural crest-derived cell. Melanocytes contain a unique intracytoplasmic organelle, the melanosome, which is the site of melanin synthesis and deposition.⁵ The melanin production within these melanocytes is a three-stage process, which involves not only the production of melanosomes within the melanocyte, termed melanogenesis, but also the trafficking and transfer of these pigment granules via long arborizing dendrites to surrounding epidermal keratinocytes. Each epidermal melanocyte, together with the epidermal cells that it serves, comprises an “epidermal melanin unit.” Each melanocyte serves 36 keratinocytes.^{6,7} Compared with lightly pigmented skin, darkly pigmented skin has melanosomes that contain more melanin and are larger; once transferred to keratinocytes, the melanosomes are singly dispersed and degraded more slowly (Table 1.1).⁸

Mechanism of melanin synthesis

The enzyme tyrosinase is critical to the formation of two subtypes of melanin. This enzyme is formed within the Golgi apparatus of the melanocyte and is transferred to

the melanosome in its first stage of development (stage I). Tyrosinase and additional proteins are assembled in stage II melanosomes. Tyrosinase first converts tyrosine to dopa, and then converts dopa to dopaquinone. The subsequent cyclization and oxidation of dopaquinone results in the brown-black, alkali-insoluble eumelanin. These chemical processes occur in the stage III and IV melanosomes.⁹ Predictably, the stage III and IV melanosomes have greater melanin content. The yellow-red, alkali-soluble pheomelanin is formed by a shunt in the eumelanin pathway; dopaquinone combines with cysteine or glutathione to ultimately form pheomelanin in the stage III and IV melanosomes. The stage IV melanosomes move from the melanocyte dendrite into the keratinocyte either as single, discrete particles or as complex, aggregated particles.^{5,9}

Melanosome transport and transfer to keratinocytes

As melanin is deposited within melanosomes, they migrate along microtubules from the cell body into dendrites in preparation for transfer to keratinocytes. Kinesin and dynein serve as molecular motors for microtubule-associated anterograde and retrograde melanosomal transport, respectively, and UVR results in augmented anterograde transport via increased kinesin and decreased dynein activity. Myosin Va, which is linked to the melanosomal RAB27A GTPase by melanophilin, captures mature melanosomes when they reach the cell periphery and attaches them to the actin cytoskeleton. After the melanosomes are transferred to keratinocytes, melanosomes are packaged in secondary lysosomes that contain acid phosphatase. Once redistributed in the keratinocytes, melanosomes are degraded by lysosomes.⁹

RACIAL AND ETHNIC DIFFERENCES IN SKIN COLOR

Defining pigmented skin or skin of color obviously entails a discussion of the various races and ethnic groups of our species, *Homo sapiens*. Skin color and the skin's reaction to such environmental factors as sunlight, as well as other obvious phenotypic manifestations, were originally used to categorize the subspecies (i.e., races) of *H. sapiens*. More recently, molecular analysis has identified genetic differences between races and ethnic groups.¹⁰

The type and amount of melanin is under the control of several genes with a great number of alleles, resulting in wide variations of skin colors. Racial and ethnic differences in skin color are related to the number, size, shape, distribution, and degradation of melanosomes. The least-pigmented human subjects are almost white and have a skin color similar to that of an albino. In contrast, the darkest-pigmented human subjects are deep brown or

Table 1.1 Melanosomes in lightly pigmented versus darkly pigmented skin.

	Lightly pigmented skin	Darkly pigmented skin
Melanization	Stages II and III	Stage IV
Size (diameter)	0.3–0.5 micron	0.5–0.8 micron
Number per cell	<20	>200
Distribution of melanosomes within lysosomes of keratinocytes	Groups of 2–10	Single
Degradation	Fast	Slow

black-brown in color. Most people of the world fall between these two extremes and are moderate brown or yellow-brown in color. The Caucasian people of Europe exhibit a light brown color that can be enhanced by exposure to sunlight. The ability to tan is marked in Mediterranean and Middle Eastern people. In contrast, some of those from the western parts of northern Europe have fair skin, red hair, and a tendency to develop red-brown freckles after exposure to sunlight.¹¹

It is probable that the amount of skin pigmentation among populations has shifted several times during the course of human natural history in response to changes in latitude, diet, body covering, and shelter. This shifting of pigmentation may have occurred relatively quickly, perhaps in a few thousand years or less. The earliest modern humans, who were in Africa, must have had dark skin, but as human migrations occurred over the course of time, skin color continually adapted to the circumstances. Thus, in the northern latitudes of Europe at the end of the last ice age, people evolved to have very light skin, which facilitated the presence of adequate calcium for these populations, despite having their dietary vitamin D diminished. On the other hand, the Inuits of the Arctic and sub-Arctic northern latitudes of Alaska, Canada, and Greenland have retained relatively dark skin, which probably has been to a large extent due to their having a continual sufficient supply of vitamin D containing fish and mammals in their diet.^{10,11}

GEOGRAPHIC VARIATION

In general, people living close to the equator are highly darkly pigmented, and those living near the poles are generally very lightly pigmented. The rest of humanity shows a high degree of skin color variation between these two extremes, generally correlating with UV exposure. The study of Gregory Barsh in 2003 correlating skin color with latitude has proven that darker skin color in humans is seen in equatorial proximity. Further, the study found that the skin reflectance is lowest at the equator and then gradually increases about 8% per 10° of latitude in the Northern Hemisphere and 4% per 10° of latitude in the Southern Hemisphere. This pattern is inversely correlated with levels of UV irradiation, which

are greater in the Southern Hemisphere than in the Northern Hemisphere.¹²

GENETICS OF SKIN COLOR

Skin color is a polygenic trait, meaning multiple genetic loci are involved in determining skin color. Multiple genes are working together to produce a continuous distribution in a “bell shape” curve of degrees of light to dark.¹³ Early models suggested two or four major genes. Recent work suggests many genes are working together in very complex, additive, and nonadditive combinations. The nonenzymatic conversion of dopaquinone into eumelanin and phaeomelanin, and their combination into melanosomes, is affected by several genetic loci. The understanding of the genetic mechanisms underlying human skin color variation is still incomplete; however, genetic studies have discovered a number of genes that affect human skin color in specific populations, and have shown that this happens independently of other physical features, such as eye and hair color. Different populations have different allele frequencies of these genes, and it is the combination of these allele variations that bring about the complex, continuous variation in skin coloration we can observe today in modern humans. Data have been collected only for *MC1R*, in which the most notable finding is a dearth of allelic diversity in African samples, which is remarkable given that polymorphism for most genes is greater in Africa than in other geographic regions.^{13,14} Thus, while *MC1R* sequence variation does not contribute significantly to variation in human skin color around the world, a functional *MC1R* is probably important for dark skin. The *TYR*, *P*, and *MATP* genes discussed earlier are well-known causes of albinism whose primary effects are limited to pigment cells.¹⁵

SEXUAL DYSMORPHISM

It has been observed that adult human females are consistently lighter in skin pigmentation than males in the same population.¹⁰ This form of sexual dimorphism is due to the requirement in human females for high amounts of calcium during pregnancy and lactation. Natural selection has led to females with lighter skin than males in all indigenous populations because women must get enough vitamin D and calcium to support the development of the fetus and nursing infant and to maintain their own health.¹²

The sexes also differ in how they change their skin color with age. Men and women are not born with different skin colors; they begin to diverge during puberty with the influence of sex hormones. Women can also change pigmentation in certain parts of their body, such as the areola, during the menstrual cycle and pregnancy, and between 50% and 70% of pregnant women will develop the “mask of pregnancy” (melasma or chloasma) in the cheeks, upper lips, forehead, and chin.¹² This is caused by increases in the female hormones estrogen and progesterone, and it can develop in women who take birth control pills or participate in hormone replacement therapy.

SKIN COLOR AND SKIN TYPING

The skin phototype (SPT) system has been used classically by dermatologists to categorize all people, including those with pigmented skin. This system, developed by Fitzpatrick, is predicated on the reactions or vulnerability of various types of skin to sunlight and UVR (Table 1.2).¹⁶ This classification system was initially developed to categorize white skin; all skin of color was initially classified as skin types I to III. Obviously, skin of color encompasses greater color gradations. Subsequently, skin of color was divided into three groups: types IV, V, and VI.

MEASUREMENT OF SKIN COLOR

There are sophisticated instruments for providing objective measurements, and these are reliable and have been proven as valid for the evaluation of skin color. Multiple studies have used reflectance spectroscopy for objective measurement of skin color.^{17,18} Two types of skin reflectance spectrophotometers have been used to determine skin color: a tristimulus reflectance colorimeter, such as the Minolta Chroma Meter (using the Commission International d'Eclairage [CIE] lab system), and a narrowband reflectance spectrophotometer, such as the Mexameter (using erythematic and melanin indices).¹⁹ However, these instruments are expensive and inconvenient for clinical use.

SKIN COLOR AND VITAMIN D

The most popular theory affirms the fact that the protection offered by dark skin from UV irradiation becomes a liability in more polar latitudes due to vitamin D3 deficiency. On sun exposure, 7-dehydrocholesterol in the skin gets converted to previtamin D3, and subsequent to that, vitamin D3 at body temperature.¹³ An increased level of melanin in the skin necessitates a prolonged exposure to UV to synthesize an adequate amount of previtamin D3. Deeply melanized skin becomes a burden and non-adaptative for the above purpose. Vitamin D3 is essential for normal growth, calcium absorption, and skeletal development. Deficiency of the vitamin can cause death, immobilization, or pelvic deformities.²⁰ Vitamin D3 is essential during pregnancy and lactation because of the need for enhanced maternal absorption of calcium in order to

build the fetal and neonatal skeletal system. It has been reported that migrants from Ethiopia to Israel, or from the Indian subcontinent to urban centers of Europe, are at risk of vitamin D3 deficiency and its manifestations.²¹ Depigmentation of the skin was a necessary adaptation for humans to inhabit outside tropics. It was argued that deeply pigmented skin was also an adaptation for physiological regulation of vitamin D3 levels. Highly pigmented skin prevents UVR-induced vitamin D3 toxicity caused by oversynthesis of previtamin D3. However, many challenged this postulate, as vitamin D3 toxicity is prevented by photolysis.²²

Vitamin D3 toxicity can occur as a result of systemic overdosing of the vitamin, and no single case of naturally occurring vitamin D3 toxicity as a result of sun exposure has ever been reported.

SKIN COLOR AND FOLATE

Another theory linked to skin color variation is folate metabolism. The folate is very sensitive to UVR. It has been proven that photolysis of the folate occurs in humans when the serum of light-skinned subjects is exposed to simulated natural sunlight.²³

Folic acid is an essential nutrient that is required for nucleotide and therefore DNA synthesis. Folate deficiency may lead to macrocytic megaloblastic anemia, bone marrow maturation, and impaired development of red blood cells. In nonhuman primates, folate deficiency is known to produce fetal abnormalities and multiple organ malformation.²³

Further, it has also been established that there is connection between folate metabolism and neural tube defects (NTDs) in humans. The records in developed countries show that anencephalus and spina bifida were common in light-skinned populations. These defects caused about 15% of all perinatal and 10% of postperinatal mortality in the worst-affected populations before introduction of preventive nutritional supplementation. Folic acid prevents 70% of NTDs in humans.²³ Besides this, folate is also essential for reproduction and spermatogenesis. Highly melanized integument is established to protect the folate photolysis in individuals of marginal nutritional status.

SKIN COLOR AND PHOTOAGING

Skin photoaging is the gradual deterioration of cutaneous structure and function following long-term recurrent exposure to sunlight or artificial UVR sources. These events are superimposed on intrinsic chronological skin aging.⁹ The epidermis and dermis are both affected, probably principally by ultraviolet B (UVB), but the dermis may be affected to some extent by ultraviolet A (UVA). Cutaneous fine and coarse wrinkling, dryness, coarseness, telangiectasia, yellowness, mottled pigmentation, laxity, loss of tensile strength, and comedones are characteristics. The role of melanin in the skin is to absorb and scatter energy from UV light to protect the epidermal cells from damage. Melanin provides considerable protection from sun damage, and the degree of protection corresponds directly to the degree of

Table 1.2 Characteristics of different skin phototypes, namely, response to sun exposure, with I fairest and VI darkest.

Type	Typical features	Tanning ability
I	Pale white skin, blue/hazel eyes, blond/red hair	Always burns, never tans
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white	Tans after initial burn
IV	Light brown skin	Burns rarely, tans darkly
V	Brown skin	Rarely burns, tans easily
VI	Dark brown or black skin	Never burns, always tans darkly

pigmentation. This sun protection offers significant prevention of photoaging in skin types IV and V. Skin types I and III are at increased risk of sun damage, photoaging, and melanoma and nonmelanoma skin cancers (NMSCs).²⁴

SKIN COLOR AND CANCER

The most important factor related to development of cutaneous neoplasms appears to be skin phenotype,^{25–29} but other factors also play a significant role. As an example, the incidence of NMSC is about 10 times higher in white than in Hispanic men, and five times higher in white than in Hispanic women. Dark skin with large concentrations of melanin protects against UV light and skin cancers; light-skinned people have about a 10-fold greater risk of dying from skin cancer than dark-skinned persons, under equal sunlight exposure (Table 1.3).

SKIN COLOR AND TANNING

Tanning is a two-stage acclimatizational response of the skin to increasing levels of UV exposure. Immediate tanning or immediate pigment darkening (IPD) is the transient brownish tan following exposure to UVA and visible light. It reaches a maximum within 1–2 hours after exposure and fades between 3 and 24 hours after exposure. No new melanosomes are formed in IPD, so the likely mechanism is the photooxidation of existing melanin or other epidermal elements.^{30,31} Delayed tanning is the durable browning caused by repeated exposure, primarily to UVB, but UVA and visible light also play a role. It is a gradual process of skin darkening, starting 48–72 hours after irradiation, and reaches a maximum 19 days after an exposure. It requires 9½ months for skin to return to its original melanin content. Likely mechanisms implicated are melanocyte enlargement, increased dendrite density, increased number of melanosomes, and melanization.^{30,31}

SKIN COLOR AND DISCRIMINATION

Discrimination based on skin color, or colorism, is a form of prejudice or discrimination in which human beings are treated differently based on the social meanings attached

to skin color. Colorism can be found specifically in parts of Africa, Southeast Asia, East Asia, India, Latin America, and the United States.³² The abundance of colorism is a result of the global prevalence of “pigmentocracy,” a term recently adopted by social scientists to describe societies in which wealth and social status are determined by skin color. Throughout the numerous pigmentocracies across the world, the lightest-skinned people have the highest social status, followed by the brown-skinned, and finally the black-skinned, who are at the bottom of the social hierarchy. This form of prejudice often results in reduced opportunities for those who are discriminated against on the basis of skin color.³³

DISORDERS OF SKIN COLOR

Uneven pigmentation of some sort affects most people, regardless of bioethnic background or skin color. Skin may appear either lighter or darker than normal, or lack pigmentation at all; there may be blotchy, uneven areas, patches of brown to gray discoloration, or freckling. Decreased pigmentation is called hypopigmentation. Increased pigmentation is called hyperpigmentation.

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Table 1.3 Influence of skin color on epidemiology of nonmelanoma skin cancer.

Characteristics	Lightly pigmented individual	Darkly pigmented individual
NMSC incidence	230/100,000	3.4/100,000
BCC:SCC ratio	4:1	1.1:1
% BCC developing in head and neck region	60–80	90
% of SCC developing in head and neck region	65	35
% of skin cancer death due to NMSC in persons <50 years of age	10	70

Note: BCC = basal cell carcinoma; SCC = squamous cell carcinoma.

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The melanocyte and melaninogenesis

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THE MELANOCYTE

Melanocytes are pigment-producing cells that are located in the basal layer of the epidermis and hair follicles.¹ Melanocytes populate the skin after migration of neural crest precursor cells, the melanoblasts, between the 12th and 14th week of intrauterine life. Melanoblasts also migrate to hair follicles, the iris, the ciliary body, the inner ear cochlea, and choroids.^{2,3} They progressively differentiate to mature melanocytes during embryogenesis and in the neonatal period. Melanosomes are present only in the differentiated melanocyte.⁴

A typical melanocyte is a branched cell that consists of an irregular, central nucleus, and an expanded cytoplasm.⁴ The cytoplasm has several branches known as dendrites (Figure 2.1). Dendrites transfer melanosomes, specialized organelles in which melanin is synthesized in the melanocyte, into the other skin cells of the epidermis.⁵ The process of melaninogenesis is completed in specific epidermal units, composed of a melanocyte and surrounding keratinocytes (1 melanocyte is in contact with 40 keratinocytes) and regulated by a closed paracrine system.⁶ Melanin is the most important determinant of skin, eye, and hair color and protects against ultraviolet (UV) damage in human skin. Particularly in the eyes, melanin has a protective role against both UV and high-frequency visible light (VL), and for this reason, people with blue, green, or gray eyes are at high risk for sun-related visual problems. In the skin, dendrites are directed toward the epidermis and the transfer of the melanosomes to the other cells is accomplished by penetrating into the basal and spinous layers.⁴ Typically, the melanocyte has a length of 7 μm , although its size may vary. The human skin has 1000–2000 melanocytes/ mm^2 , and melanocytes represent 5%–10% of the cells of the basal layer of the epidermis. The ratio of melanocytes to keratinocytes is 1/10 in the epidermal basal layer and 1/5 in the hair follicles.¹ The number of melanocytes varies at different body sites. In the skin of the palms and soles, the melanocyte density is 10%–20% of the density of melanocytes in the skin of the trunk.⁷ In the hair follicle, melanocytes go through cyclic modifications in fine-tuning with the hair cycle. During the anagen phase, they are located in the proximal hair bulb, and from there, they have the capacity to proliferate, migrate, and undergo maturation. Throughout the anagen phase, the process of melaninogenesis is implemented and the transfer of melanin to the keratinocytes takes place. Finally, during the late catagen phase, apoptosis of melanocytes occurs.⁸

MELANINOGENESIS

Melaninogenesis is a complex process with different stages that leads to the production and transportation of melanin.⁹ The process of melaninogenesis is completed in three stages. The first stage is the addition of cysteine to dopaquinone and the production of cysteinyl-dopas. The second stage is the production of pheomelanin by the oxidation of cysteinyl-dopas, and the third stage is the production of eumelanin. The eumelanin/pheomelanin ratio is affected by cysteine concentration and tyrosinase activity.¹⁰ Pigmentation defects, classified as hypo- or hyperpigmentation, could be caused by an alteration during the process of melaninogenesis.⁹ There are several pathways, proteins, and mechanisms that regulate melaninogenesis and several melanogenic inhibitors.

Pathways regulating melaninogenesis

The process of melaninogenesis is regulated by a variety of pathways. The most important are the cyclic adenosine monophosphate (cAMP)-dependent and the protein kinase C (PKC)-dependent pathways, but additional pathways may also contribute to this process.⁸ The cAMP-dependent pathway modulates melaninogenesis by activating the protein kinase A (PKA), a serine/threonine kinase that consists of two catalytic and two regulatory subunits¹¹ and phosphorylates several regulatory proteins, enzymes, and ion channels during this process.¹² cAMP also modifies other pathways, like the phosphatidylinositol (PI) 3-kinase pathway, that ultimately serve to control melaninogenesis. PKC is a serine/threonine kinase that is activated by diacylglycerol and via its pathway induces phosphorylation of key proteins of melaninogenesis, such as tyrosinase. Additional pathways include those that increase intracellular cAMP levels, pathways that are activated by cyclic guanosine monophosphate (cGMP) and nitric oxide (NO), and the mitogen-activated protein kinase (MAPK)-related pathway, which phosphorylates proteins like microphthalmia-associated transcription factor (MITF).^{8,13,14}

Regulatory proteins

The key enzymes that play a central role in melaninogenesis are tyrosinase, tyrosinase-related enzymes 1 and 2 (TRP-1 and TRP-2) and PKC- β .¹⁵ Tyrosinase is the most important enzyme for melaninogenesis. It is a glycoprotein of the melanosomal membrane and consists of three domains, an internal melanosomal, a short transmembrane, and a cytoplasmic domain. The cytoplasmic domain is composed of 30 amino acids and participates in the transport of the

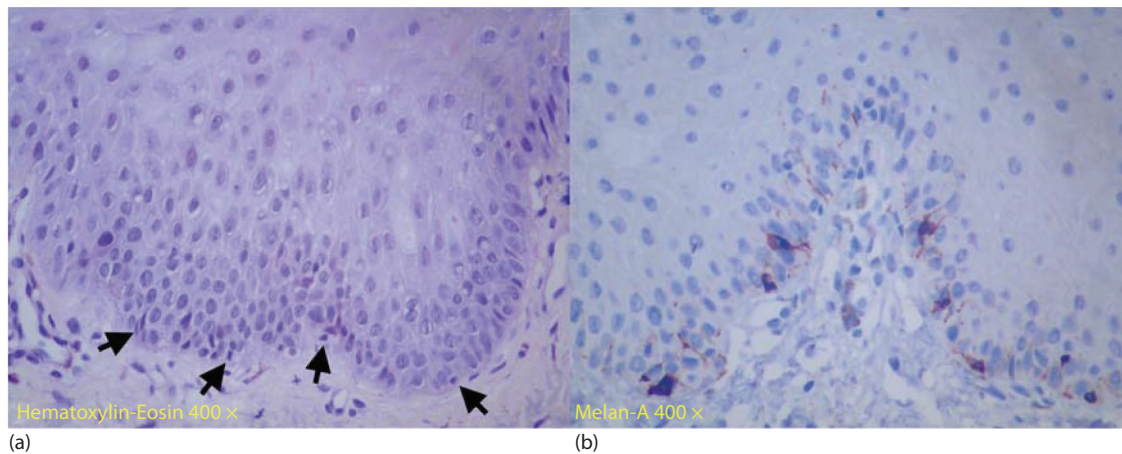


Figure 2.1 Detailed histological view of a melanocytic macule of oral skin lip. (a) Stain with hematoxylin-eosin $\times 400$. (Arrows show melanocytes.) (b) Stain of melanocytes with the melanocytic differentiation marker Melan-A $\times 400$. (Courtesy of Dr. V. Haniotis.)

enzyme from the nucleus to melanosomes.¹⁶ The internal melanosomal domain contains the catalytic region that represents almost 90% of the protein and has histidine residues. These residues bind with copper ions that are required for tyrosinase activity. Tyrosinase catalyzes the conversion of L-tyrosine into L-3,4-dihydroxyphenylalanine (L-DOPA) during melanin synthesis.¹⁷ Importantly, mutations that inactivate tyrosinase are present in the most severe form of albinism. In addition, in several ultrastructural studies, the reduction of tyrosinase levels inhibited the expression of genes that regulate melaninogenesis, as well as the accumulation of terminal melanosomes.¹⁸

TRP-1 and TRP-2 are two enzymes with 40% amino acid homology to tyrosinase, and they are also located in the melanosomal membrane. Their precise role is unclear. Possibly, TRP-1 plays a role in the synthesis of melanosomes and the activation and stabilization of tyrosinase. It is further possible that TRP-1 increases the eumelanin/pheomelanin ratio. TRP-2 converts DOPACHrome to 5,6-dihydroxyindole-2-carboxylic acid (DHICA) during melanin synthesis, and for its activation zinc ions are required.^{19,20}

PKC- β is involved in the stabilization of tyrosinase and the increase of its enzymatic activity by phosphorylating serine residues on the cytoplasmic domain of tyrosinase. This process seems to lead to the formation of a complex between tyrosinase and TRP-1, which results, as mentioned in the previous paragraph, in the activation and stabilization of tyrosinase. Two further proteins that regulate melaninogenesis are the transcription factor MITF and the melanocortin 1 receptor (MC1R). MITF is very important for the survival of the melanocyte. It is a basic helix-loop-helix and leucine zipper transcription factor, and it has at least nine isoforms. MITF blocks the apoptotic process by enhancing the expression of BCL2, a major antiapoptotic protein in the cell.²¹ Additionally, it regulates the transcription of the most important melaninogenesis enzymes, PKC- β , tyrosinase, TRP-1, and TRP-2. More specifically, transcription of PKC- β and tyrosinase is controlled by the MITF-M isoform.²² MC1R

is the first of the five proteins that belong to the family of the melanocortin receptors, which are G protein-coupled receptors.⁹ The remaining are MC2R, MC3R, MC4R, and MC5R. Each of them has seven transmembrane domains. MC1R is expressed mostly in melanocytes, but also in other types of cells (keratinocytes, fibroblasts, and endothelial cells).⁸ It is activated by the hormones ACTH and α -MSH. MC1R regulates melaninogenesis by activating PKA, which induces MITF transcription, and then MITF, by the processes mentioned above, promotes synthesis of eumelanin.¹⁵

Several ion channels seem to have specific roles in melaninogenesis. These channels function at the plasma membrane and at the membrane of intracellular organelles of the melanocytes. The three most important ion channels that operate across the plasma membrane and modulate pigmentation are TRPM1, TRPM7, and TRPA1. They all belong to the transient receptor potential (TRP) channel family. TRPM1 levels are associated with basal pigmentation, according to the fact that a reduction of TRPM1 expression leads to decreased cellular melanin content. TRPM1 expression is controlled by MITF. On the other hand, TRPA1 is activated by ultraviolet A (UVA) and contributes to a rapid increase of melanin. The exact role of TRPM7 in melaninogenesis remains unknown. The most important intracellular ion channels are the endolysosomal TRPML channels, which belong to the mucolipin (ML) subfamily of TRP channels and regulate melanosomal function; the TPC (two-pore channels), which are expressed in acidic organelles and are regulators of melanosomal physiology and pigmentation; and the ClC-7 (chloride channels, isoform 7), which affect the melanosomal differentiation. There are also melanosomal-specific ion channel proteins that regulate at various steps the melaninogenesis that takes place in the melanosome. The most important of them are OCA2, SLC45A2, SLC24A5, and the OAI ATPases.²³ Finally, mitochondrial dynamics regulate melaninogenesis by accelerating degradation of MITF,

via modulation of the signaling pathway reactive oxygen species (ROS)–ERK.²⁴

Ultraviolet radiation

Ultraviolet radiation (UVR) (wavelengths 100–400 nm) is considered the most important extraneous regulator of melaninogenesis.⁹ It is divided into UVA (320–400 nm), ultraviolet B (UVB) (280–320 nm), and ultraviolet C (UVC) (100–280 nm). Normally, the majority of UVA (more than 95%) and only 1%–10% of UVB reaches the earth's surface, and almost 100% of UVC is absorbed by the atmosphere and the ozone layer.²⁵ UVR is considered to be the main causative factor of skin cancers, like basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma.⁷ There has been a dramatic decrease of the ozone layer during the last decades, and it has been estimated that a reduction of 1% in ozone layer increases melanoma mortality by 1%–2%.²⁶ Although UVB radiation is considered more mutagenic and cytotoxic than UVA, UVA penetrates deeper into the skin, and it is not filtered by window glass. Interestingly, almost 50% of the UVA exposure of an individual occurs in shadows. UVR causes several acute and chronic effects on the skin. The most known chronic effects are photoaging and photocarcinogenesis. The main acute effects of UVR are erythema (induced mainly by exposure to UVB), photodamage, immunosuppression, mutations, vitamin D synthesis, and facultative skin color (tanning).⁷ The latter is also known as induced pigmentation. There are two types of induced pigmentation, the immediate and the delayed type. The immediate type is independent of melanin production, caused by the UVA wavelengths, and it appears 5–10 minutes after exposure to UVA radiation. It lasts minutes to days. The delayed type occurs 3–4 days after the exposure and disappears within weeks; it is mainly due to UVB and less to UVA exposure and is the result of an increase in the levels of epidermal melanin.⁹

UVR affects melaninogenesis both directly and indirectly. UV exposure can cause direct DNA damage in keratinocytes, which is the key step for triggering melaninogenesis, followed by the activation of p53. p53 is a tumor suppressor protein playing a central role in melaninogenesis. After its activation, p53 increases the level of tyrosinase and the release of α -MSH.^{9,25} UVA causes indirect DNA damage by inducing ROS, whereas UVB acts directly and induces structural DNA damage by forming DNA photoproducts, mainly thymine dimers and pyrimidine(6–4)pyrimidone.^{15,27} DNA damage occurring immediately after an exposure to UVR is more prolonged, and DNA starts repairing shortly after this.⁷ All these mechanisms stimulate melaninogenesis in a direct manner, by increasing the proliferation of melanocytes, the transfer of melanosomes, the number of dendrites, and the level of melanogenic enzymes.²⁸ An indirect mode of stimulation of melaninogenesis by UVR constitutes the induction of paracrine factor production by epidermal cells acting on neighboring melanocytes.

Not only UVR, but also VL (400–700 nm) regulates melaninogenesis through a photoadaptive response, according to *ex vivo* and clinical studies. The *ex vivo* studies showed that exposure to VL increases tyrosinase activity and melanin formation and also alters the expression of pigmentation-related genes in skin explants. The clinical studies showed that multiple exposures to VL induce pigmentation *in vivo*. VL induces both transient (after a single exposure) and long-lasting pigmentation (after multiple exposures). The long-lasting pigmentation can last for more than 8 weeks, depending on the total dose of the VL.²⁹

Paracrine melanogenic regulators

There is a complex system of hormones, growth factors, and cytokines in epidermal cells, most of them being influenced by UVR, which affect melaninogenesis.⁷ The most important stimulators are endothelin 1, inflammatory mediators (prostaglandins, leukotrienes etc.), proopiomelanocortin (POMC) and derived peptides (ACTH and α -MSH), stem cell factor (SCF), catecholamines, neutrotrophins, basic fibroblast growth factor (bFGF), and NO.¹⁵ As mentioned before, ACTH and α -MSH increase skin pigmentation by activating MC1R. These hormones were discovered by Dr. Aaron Lerner in the 1950s, and their expression is inducible by UVR and mediators present in skin during cutaneous inflammation, such as cytokines and interleukins (ILs).³⁰ α -MSH also increases skin pigmentation by blocking 6BH4, an inhibitor of tyrosinase activity.³¹ SCF, a cytokine that binds to the c-Kit receptor and is important for the formation of blood cells, regulates melaninogenesis by binding to the c-Kit tyrosine kinase receptor. This binding leads to the activation of MAPK. MAPKs are responsible for the activation (phosphorylation) of MITF.¹⁵ bFGF is produced by keratinocytes after exposure to UVB and induces the mitogenic effect of tyrosine kinase receptors. bFGF is one of the first melanocyte mitogens identified.³² Inflammatory mediators stimulate skin pigmentation by upregulating tyrosinase levels and increasing the dendricity of melanocytes.³³ Endothelin 1, a vasoconstrictor that is produced by vascular endothelial cells, activates tyrosinase, increases the levels of TRP-1, and reduces UV-induced apoptosis. It also stimulates melanocyte proliferation by acting synergistically with α -MSH and bFGF.⁷ Catecholamines induce melaninogenesis through cAMP-dependent or PKC- β pathways.³⁴ Neutrotrophins, proteins that induce survival, function, and development of neurons, reduce the cell death of melanocytes by increasing the levels of the antiapoptotic protein Bcl2, after exposure to UVR.¹⁵ NO is produced in keratinocytes by UVR, and it increases tyrosinase activity.³⁵

Differences in skin pigmentation are the end result of the melanogenic activity; the total number, size, and packaging of melanosomes; and the type of melanin produced in melanosomes, and not the total amount of melanocytes. However, the mechanisms leading to human skin and hair color variation are not fully understood yet.¹⁸

Melanosomes in dark skin are more numerous, and have larger axes than in white skin since the time of birth.³⁶ Interestingly, black skin allows 7.4% of UVB and 17.5% of UVA to penetrate, while white skin allows 24% of UVB and 55% of UVA to pass through. This means that melanin in black skin is three times as effective as that in white skin in inhibiting UVR from penetrating.⁷

Other melanogenic stimulators

Angiotensin II, a hormone that causes vasoconstriction, stimulates melaninogenesis (via the PKC pathway) by increasing tyrosinase activity and finally synthesis of melanin.³⁷ RUTBC1, a Rab9-binding protein, regulates the trafficking of melanogenic enzymes in melanocytes by functioning as an inactivating enzyme GAP (GTPase-activating protein), which inactivates two cell type-specific Rab proteins (Rab32 and Rab38). The inactivation of these Rab proteins regulates the trafficking of melanogenic enzymes.³⁸

Many common drugs have an effect on melaninogenesis. The most known are antiepileptic agents (hydantoins), antibiotics (such as tetracyclines), diuretics, chloroquine, levodopa, nonsteroidal anti-inflammatory drugs, oral contraceptives, some chemotherapy agents (doxorubicin, cyclophosphamide, and others), and heavy metals.⁶ (E)-4-(3,4-Dimethoxyphenyl)but-3-en-1-ol (DMPB), which is a component of a tropical ginger of Southeast Asia named *Zingiber cassumunar* Roxb, seems to trigger tyrosinase expression and activity, to increase dendrite formation, and finally, to increase melanin synthesis in human melanocytes.³⁹

Melanogenic inhibitors

Hyperpigmentation is considered a major cosmetic problem, and inhibition of melaninogenesis could provide a treatment concept for this disorder. This is the main reason why many studies focus on the identification of inhibitors of melaninogenesis and their mechanisms. There is a family of inhibitors that includes benzimidazole-2-thiols, phenylthiols, phenylthioureas, tibolone metabolites, oligopeptides, resorcinol derivatives, 4-phenylimidazole-2-thiones, and siRNA oligomers. These inhibitors act by reducing the activity of tyrosinase. There are inhibitors of adaptor protein (AP) complexes. These inhibitors decrease the expression of melanogenic enzymes and block the maturation of melanosomes, by interrupting the transport of melanogenic enzymes toward the melanosomes.

Several inhibitors of melanin formation have been reported, such as *para*-aminobenzoic acid (PABA), quinolines, and benzopyrone.⁴⁰ Melaninogenesis is also inhibited by hormonal inhibitors and their receptors. These inhibitors include melanocortin's antagonists, growth factor cytokines and their receptors, G protein-coupled receptors, and other negative regulators. Melanocortin's antagonists are the melanin-concentrating hormone, the Agouti protein, and the Agouti modifiers. The growth factor cytokines that inhibit melaninogenesis are IL-1, IL-6, interferon (IFN)- α , and IFN- γ and their receptors,

and tumor necrosis factor (TNF)- α , TNF- β , and transforming growth factor (TGF)- β 1 and their receptors. The G protein-coupled receptors are serotonin, melatonin, dopamine, and acetylcholine and their receptors. Other known negative regulators are the thyroid gland hormones and vitamin E.¹² Epidermal growth factor (EGF) and tranexamic acid diminish laser-induced melaninogenesis. Although the mechanism of diminution of melaninogenesis by EGF is not known yet, tranexamic acid reduces melanin contents and tyrosinase activity.^{41,42} Pleiotrophin (a secreted heparin-binding protein) inhibits melaninogenesis through MITF degradation via the Erk1/2 activation in melanocytes.⁴³ Finally, proton pump inhibitors (PPIs) seem to inhibit melanin biosynthesis via the down-regulation of melaninogenesis-associated genes.⁴⁴

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Melanin

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HISTORICAL BACKGROUND

In humans, melanin is the main pigment responsible for the various patterns of pigmentations in skin, hair, and eyes. In addition, melanin has been found in a variety of other tissues, such as the inner ear and brain. Cutaneous melanin plays a critical role in camouflage, mimicry, social communication, and protection against harmful effects of solar radiation.¹ Melanin is the most ubiquitous, resistant, heterogeneous, and ancient pigment found in nature. It appeared very early in most living creatures on the earth, as it has been identified in old fossils from dinosaurs, early birds, nonavian theropod species,^{2,3} and primitive cephalopods.⁴

The term *melanin* originates from the ancient Greek *melanos*, meaning “dark.” *Melanin* was probably first used by the Swedish chemist Berzelius in 1840 to refer to a dark pigment extracted from eye membranes.^{5,6} However, the first references of human skin pigmentation without using the term *melanin* were found in the descriptions of some pigmentary disorders in pharaonic medicine in the Ebers Papyrus (1550 BC),⁷ and one of them was probably *vitaligo*, although that term appeared much later and was derived from the Latin word *vitellus*, meaning “veal” or “pale pink skin.”⁸ The first written description of skin pigmentation in history came from Herodotus in Greece, who described the darker skin of Persians, Ethiopians, and Indians in comparison with that of his nationals.

The varieties of human color could have been traced from Noah’s three sons, Shem, Japheth, and Ham (which means “black,” the characteristic color of his descendants, the Babylonians), as stated in the Bible. It was believed that hot water falling from the sky due to the proximity of the sun to the earth in some places was responsible for the dark color, until Aristotle attributed it to a prolonged exposure to sun, thus representing the first explanation of hyperpigmentation following sun exposure. In the modern era, scientists such as Malpighi in Naples and several others described a great number of anatomical descriptions of pigmentation.⁸ It has been suggested that melanin represents decomposition of hemoglobin in the European and Arabic civilizations; however, Berzelius and others showed very significant differences between melanin and hemoglobin that ruled out such a relationship, and that no difference exists in hemoglobin contents between people of different colors.^{5,9}

MELANIN

Chemical and physical properties

Melanins are a group of complex pigments that are diverse and partially undefined.^{10–12} Most of the proposed

definitions are inadequate due to the difficulty of defining a substance with such a wide diversity in composition, color, size, occurrence, and functions. This diversity is expected since melanin can be found in all living and diverse kingdoms.¹³

Mammalian melanins are the end products of complex multistep transformations of L-tyrosine to polymorphous and multifunctional biopolymers, represented by eumelanin, pheomelanin, neuromelanin, and mixed melanin pigment.^{11,14,15} Melanin biosynthesis commences either from the hydroxylation of L-phenylalanine to L-tyrosine (non-obligatory step, operative *in vivo*) or directly from L-tyrosine, which is then hydroxylated to L-dihydroxyphenylalanine (L-DOPA) (obligatory step both *in vitro* and *in vivo*) (Figure 3.1). Tyrosinase is the key enzyme of melanogenesis, and L-DOPA is the precursor for both melanins and catecholamines. Oxidation of L-DOPA to dopaquinone is common to both eumelanogenic and pheomelanogenic pathways.^{11,14}

Eumelanogenesis involves the further transformation of dopaquinone to leukodopachrome, followed by a series of oxidoreduction reactions with production of the intermediates dihydroxyindole (DHI) and DHI carboxylic acid (DHICA), with ultimate polymerization to form eumelanin (Figure 3.1).^{11,15,16} Eumelanins are black to brown, insoluble in most solvents, and more abundant in human beings, especially in dark-skinned individuals. A unique character of eumelanin is its stable paramagnetic state exerted by its semiquinone units, which are also responsible for eumelanin redox properties.¹⁷ In Caucasians, localized high cutaneous concentrations of eumelanin can be found in moles, macules, nevi, or lentigos.¹³ Eumelanins act as polyanions and can reversibly bind cations, anions, and polyamines.¹⁵

Pheomelanogenesis involves conjugation of dopaquinone to cysteine or glutathione to yield cysteinyl-dopa and glutathionyl-dopa, for further transformation into pheomelanin, which exhibits a yellow or reddish-brown color and alkali solubility (Figure 3.1).^{14–16} During the pheomelanogenesis, the amino acid L-cysteine, free or in compounds such as glutathione, is added to L-dopaquinone, the tyrosinase-catalyzed oxidized intermediate from L-tyrosine. Thus, L-dopaquinone is the branch point to form eumelanin or pheomelanin inside the melanocyte (Figure 3.1). The presence of sulfur in pheomelanins by addition of L-cysteine or glutathione is the main difference with eumelanin.^{18–21} Cysteine can be added to several positions at the dopaquinone ring, but 5-S-cysteinyl-dopa and 5-S-glutathionyl-dopa

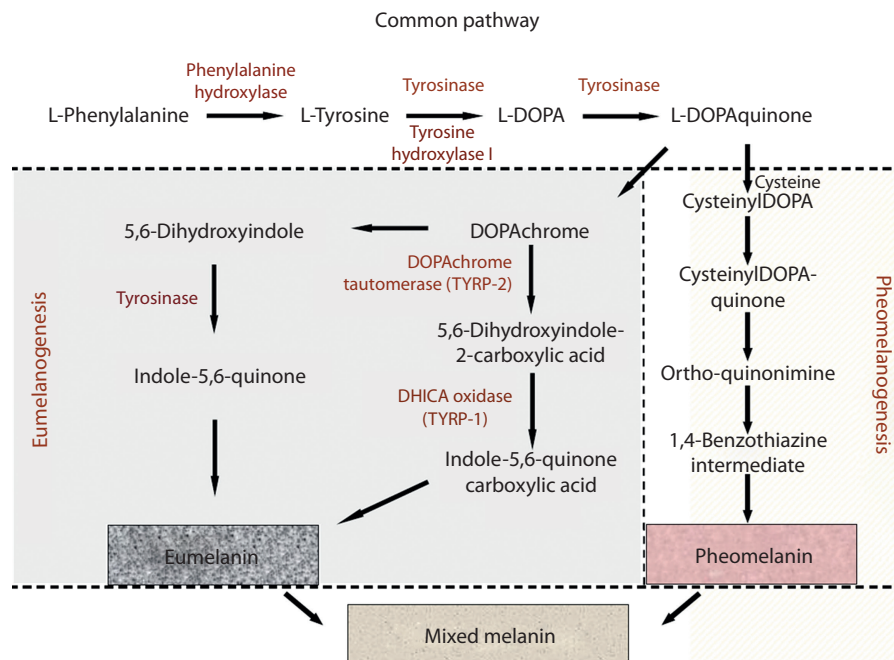


Figure 3.1 Schematic representation of the major steps in the pathway of melanin biosynthesis in the skin. DHICA, 5,6-dihydroxyindole-2-carboxylic acid; TYRP, tyrosinase-related protein.

are the predominant isomers formed.^{22,23} Pheomelanin can bind drugs and chemicals, and it contains semiquinones with additional semiquinone centers that allow its identification and quantification.²⁴ Pheomelanin is found in relatively large quantities in red hair, freckles, and nipples.¹³

Neuromelanin originates from catecholamines through several oxidation–reduction reactions *in vitro*,²⁵ whereas *in vivo*, only dopamine and cysteinyl dopamine can serve as primary precursors to the pigment.^{26,27} Neuromelanins are macropolymers composed of aminochromes and nor-adrenalinochromes and, unlike other types of melanins, are not formed in melanocytes, but in catecholaminergic neurons.^{26–28} They are a brown-black pigment with stable paramagnetic properties, insoluble in organic solvents, bleached by hydrogen peroxide, and labeled by silver stain.²⁷ They have mixed properties of both eumelanins and pheomelanins, as they chelate metals and interact with several inorganic and organic compounds.^{18,29,30} Neuromelanin has been shown to accumulate in the substantia nigra of the brain during aging.^{31,32} The function of brain neuromelanin is not known, although it may play crucial roles in apoptosis, neurodegeneration, and the related Parkinson's disease.^{32,33} It has also been shown that neuromelanins can serve as cytosolic scavengers for potentially neurotoxic subproducts such as Fe(III) or reactive oxygen species (ROS) due to oxidation of catecholamine neurotransmitters. α -Synuclein could be one of the points responsible for the positive association between Parkinson's disease and melanoma via its differential roles in melanin synthesis in melanoma cells and in dopaminergic neuronal cells.^{34,35}

Mixed melanin, on the other hand, contains both eumelanin and pheomelanin, and both can be synthesized by the same melanocyte. Other types of melanins may be generated by enzymatic oxidation of serotonin or tryptophan via tyrosinase, but the resulting products have structures different from those of classical melanin. Melanin-like substances can also result from tyrosinase-mediated transformation of opioid peptides that produce black to brown pigments with paramagnetic properties almost identical to those of DOPA melanin.³⁶

Site of melanin synthesis and storage

Melanin is synthesized and stored inside the melanosomes.³⁷ There are two main types of melanosomes, namely, ovoid eumelanosomes and spherical pheomelanosomes. Differences in the amino acid transport systems to these suborganelles control the availability of L-tyrosine and also of L-cysteine or glutathione inside the organelle and regulate the formation of eumelanin or pheomelanin.^{38–40} Melanin synthesis and confinement in the melanosomes protect melanocytes from several cytotoxic by-products, such as quinines and hydrogen peroxide.⁴¹

Differences in skin color of humans are mainly determined by melanin content, melanin composition, and melanosome size in the neighboring keratinocytes,⁴² rather than the number of epidermal melanocytes, which are almost equal in all races and ethnic groups.^{43,44} The degree of pigmentation is the final outcome of a finely tuned process that includes melanin synthesis within melanosomes, followed by their transfer and dispersion inside keratinocytes.^{44,45} Darker skin tends to have many large individually dispersed melanosomes, whereas lighter

skin contains smaller melanosomes,⁴⁶ which are aggregated and bound in groups.⁴⁷

Extracutaneous melanin

Melanin may also be produced by other cells, such as cells of pigmented epithelium of the retina, epithelia of the iris, and the ciliary body of the eye; some neurons; and adipocytes,^{48,49} thus providing an explanation for its presence in the tissue underlying the iris of the eye, in eyespots, in retinal pigment epithelia,^{50,51} and in the stria vascularis of the inner ear.⁵² In contrast to skin and hair, melanosomes remain in the melanocytes of the eye and inner ear and are not transferred to surrounding cells. Melanin has also been detected in various parts of the human body, such as the adrenal gland, heart, lungs, liver,⁵³ and lymphocytes,⁵⁴ and in the lymphatic system draining the skin.⁵⁵

Melanin metabolism

Intact mature melanosomes from basal melanocytes are engulfed by keratinocytes and via their lysosomal compartment become melanin dust in the upper nonviable layers of the epidermis. There is scant information on the actual mechanism of melanin breakdown or biodegradation, as melanin appears to be resistant to enzymatic lysis. It has been suggested that only the phagosomal NADPH oxidase can degrade melanin itself via oxidative attack.⁵⁶ On the other hand, hair eumelanogenic melanosomes tend to remain fully intact in the black hair shaft, whereas the pheomelanin granules characteristic of red and blonde hair are partially digested. Both melanin types can be synthesized and released by the same melanocyte.¹

DETECTION OF MELANIN (SPECIAL STAINS FOR MELANIN)

Several special stains facilitate the light microscopic visualization of melanocytes and their products. Silver stains reveal the presence of melanin due to its ability to combine with silver nitrate, which, upon reduction with hydroquinone to silver, stains black (argyrophilic). Also, ammoniated silver nitrate may be reduced by phenolic groups present in melanin, forming black silver precipitate (Fontana–Masson method). Both methods are not entirely specific for melanin; however, the ability of strong oxidizing agents, such as hydrogen peroxide or potassium permanganate, permits more specific identification.⁵⁷ In practice, hydrogen peroxide is used to bleach black hair, resulting in a yellow color, a procedure widely used at home and in cosmetic saloons. The DOPA reaction is used to visualize the pigment cells and is in essence an assay for tyrosinase activity in melanosomes.⁵⁸

MELANIN PIGMENT FUNCTIONS IN HEALTH AND DISEASES

As melanin is located in many tissues, and in particular all living organisms, it is not surprising that melanin has several different functions.

Normal variations and differences in skin melanization

Gender

The epidermis of adult human females is less melanized than that of adult males, suggesting a gender-specific effect.⁵⁹ This discrepancy is in favor of and facilitates the higher need for vitamin D in women that is imposed by the increased intestinal calcium absorption of pregnancy and lactation and activated in skin by ultraviolet (UV) light.⁶⁰

Age

It has been shown that melanin in skin decreases with aging.⁵⁹ The significance of this observation is not known, but it may also play a role in supplementing the necessary vitamin D to these particularly vulnerable age groups.

Health

Most of the physiological functions of melanin are related to protection against external insults, such as sunburn, and conferring environmental advantages to melanized cells. Human skin contains a mixture of all melanin types; however, the diversity of skin pigmentation among different ethnic groups depends on the ratio of eumelanin to total melanin content.¹ Although pheomelanin does not correlate with skin pigmentation, as a similar amount of this pigment exists in dark and light skins, the ratio of eumelanin to pheomelanin determines the color of hair.⁶¹

Eumelanin shows a very broad UV-visible absorption spectrum, and it is able to dissipate up to 90% of the absorbed energy from sunlight radiation. It has already been shown that cutaneous melanin is a very efficient photoprotective factor and is considered a natural sunscreen that functions as a broadband radiation absorbent. Thus, melanin protects the skin from the potentially damaging effects of UV light. Exposure of human epidermis to sunlight produces melanin, causing a moderate tan effect on the skin to increase the amount of photoprotective pigment.⁶² Many epidemiological studies have shown a lower incidence of skin cancer in individuals with a high amount of melanin in the skin.^{63,64} Skin is the most common site of cancer in humans, especially in those with pale skin, and UV is the main environmental factor responsible for the formation of malignant melanoma and other skin cancers.⁶⁵

Tanning also protects skin from UV radiation damage of sweat glands and the resultant suppression of sweating and abnormal thermoregulation,⁶⁶ carcinogenesis, and nutrient (e.g., folate) inactivation by photodestruction.⁶⁷ On the other hand, humans living in areas with lower UV levels adapt with lesser pigmentation, which protects against vitamin D3 deficiency.⁶⁸ Additional benefits of melanin may include a bactericidal potential via the production of orthoquinones.⁶⁹

Melanin in hair also has several benefits. It protects from sunstroke, and chelates and traps chemicals, toxins, and heavy metals, thus diluting and minimizing their

access to living tissues.^{70,71} In addition, hair melanin contributes to the tensile strength of hair via cross-linking with proteins.¹

In the eye, melanin seems to modulate the beams of light entering the eye and the retinal pigment epithelium (RPE) attached to the retina. It has been suggested that melanin allows better visual acuity by absorbing scattered light within the eye.⁷² Similarly, melanin of the iris and choroid protects the retina from intense sunlight, which otherwise would disturb visual acuity, as seen in humans with blue or green eyes and albinism. In turn, it has been shown that the antioxidant properties of melanin protect components of RPE, such as A2E, from photooxidation.⁷³ Moreover, melanization of RPE may also be implicated in the downregulation of rod outer segment phagocytosis. This phenomenon has been partially related to foveal sparing in macular degeneration⁷⁴ because of the change in the redox properties. RPE melanin has been proposed to turn from a normally antioxidant polymer into a prooxidant. The peculiar pattern of iris melanin appears to be a reliable tool in personal identification.⁷⁵

It has also been shown that the intermediate cells of the stria vascularis of the cochlea are melanocytes, and that they play a crucial role in hearing function.⁷⁶

Neuromelanins have mixed properties of both eumelanins and pheomelanins, as they chelate metals and interact with several inorganic and organic compounds.^{29,30} It has also been shown that neuromelanins accumulate in the substantia nigra of the brain during aging.^{31,32} The function of brain neuromelanins is not definitely known, although they can serve as a cytosolic scavenger for potentially neurotoxic subproducts, such as Fe(III) or ROS, due to oxidation of catecholamine neurotransmitters.³²

Melanin role in pigmentary and nonpigmentary disorders

The main action of melanin in human skin appears to be attenuation of UV penetration to skin and protection against DNA damage and carcinogenicity. Eumelanins are considered to be more effective in terms of photoprotection than the reddish pheomelanin. Pheomelanin, in contrast to eumelanin, is photolabile and easily involved in the production of superoxide, and cannot effectively scavenge all the derived carcinogenic ROS.^{77–79} As a consequence, the risk of skin cancer in lighter skin is 30- to 40-fold higher than in darker skin.⁸⁰ It has been suggested that postinflammatory hyperpigmentation is a reactive process in which the increased melanin synthesis and deposition sequester the intrinsic or extrinsic toxic and hazardous substances, highlighting the importance of melanin for skin homeostasis.⁸⁰

The most common pigment disorders are not disorders of melanin, but rather of the pigment-producing cell itself, which may be absent, reduced in number, or hyperactive. Hypomelanosis can be either congenital, via inheritance of mutations in pigment-related genes, e.g., albinism and piebaldism, or acquired, e.g., vitiligo. Also, phototype I skin, red hair, and severe obesity characterize rare

syndromes associated with homozygous mutations in the proopiomelanocortin and prohormone convertase 1 genes, respectively.⁸¹ On the other hand, hypermelanosis can be associated with inflammatory responses, such as postinflammatory hyperpigmentation, or with local abnormal melanocyte function, such as melasma, dysplastic nevi, or melanotic melanoma.¹³

It has been shown that loss-of-function mutations of the MITF gene cause Waardenburg syndrome type 2 (WS2),⁸² whereas a dominant negative mutation of MITF causes Tiez syndrome, i.e., albinism–deafness syndrome, whose symptoms are similar to WS2 but more severe.^{83,84} In both syndromes, MITF mutations often cause hearing impairment, along with skin and iris pigmentation anomalies. Both the pigmentation anomaly and the hearing impairment are caused by the absence of melanocytes.⁷⁶ On the other hand, melanin liberated from rubbing of the pigmented iris epithelium against lens structures results in reduced aqueous outflow with the risk of glaucoma, a condition called pigment dispersion syndrome.⁸⁵

In principle, neuromelanins seem to be a waste product of catecholamine metabolism, as the amount of cytoplasm within catecholamine neurons occupied by neuromelanins was found to increase progressively with the brain's age.³² Nevertheless, it has been shown that neuromelanin may play crucial roles in apoptosis, neurodegeneration, and the related Parkinson's disease.^{32,33} α -Synuclein could be one of the points responsible for the positive association between Parkinson's disease and melanoma via its differential roles in melanin synthesis in melanoma cells and in dopaminergic neuronal cells.^{34,35}

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Pathophysiology of hyperpigmentation

4

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Hyperpigmentation is a complex process that occurs in physiologic and pathologic states in response to complex signaling cascades and a variety of stimuli, including ultraviolet (UV) radiation, inflammation, hormones, and medications. Skin pigmentation begins with the synthesis of melanin within melanocytes, which is then transferred to neighboring keratinocytes, where it is translocated to the upper pole of the nucleus and degraded as the keratinocyte undergoes terminal differentiation.^{1,2} There are numerous genetic disruptions involved in melanocyte migration during embryogenesis, melanin synthesis, and melanosomal function that can lead to elevated melanin production.^{1,3} Although the exact pathogenesis of most hyperpigmentation disorders is unknown, several pathways have been identified as key defects that lead to hyperpigmentation, including melanocyte-stimulating hormone (MSH)/cyclic adenosine monophosphate (cAMP), KIT, and Wnt signaling pathways.³

Hypermelanosis is a pathologic state in which there is an increase of melanin as a result of an increased number of melanocytes in the epidermis (melanocytotic hypermelanosis) or an increased production of melanin (melanotic hypermelanosis).² Melanocytotic hypermelanosis involves alterations in the mitotic division of melanocytes and is seen in benign and malignant melanocytic neoplasms, including lentigo, lentigo maligna, lentigo maligna melanoma, superficial spreading melanoma, and nodular melanoma. Melanotic hyperpigmentation is defined by an increase in the production of melanin without a significant increase in the number of melanocytes. This type of hypermelanosis is seen in melasma, ephelides, café-au-lait macules (CALMs), and Addison's disease.^{2,4}

Globally, alterations in pigmentation are a result of genetic defects, hormonal changes, and/or UV radiation. For example, melasma, a disorder of hyperpigmented patches on the face and less commonly dorsal forearms, is thought to be a result of a combination of these factors. Melanocytes in sites of melasma are thought to have estrogen receptors that stimulate these cells to become hyperactive.^{2,5} Additionally, it has been reported that when the epidermis of these lesions is dermabraded, the melanocytes that repopulate the area have the same hypermelanotic state, suggesting a special clone of cells.²

Hypermelanosis can be classified clinically and histologically into epidermal and dermal subtypes. Epidermal hypermelanosis results from an inflammatory response secondary to dermatitis, UV exposure, hormones, medications, and/or injury. This is known as inducible melanin pigmentation. As a result of these triggers, arachidonic acid is released and oxidized into prostaglandins (PGE), leukotrienes (LTC), thromboxanes (TXB), and other products.

There is evidence that autocrine and paracrine cytokine networks exist between melanocytes and keratinocytes, which contribute to melanocyte stimulation and function.^{6,7} Specifically, LTC₄, LTD₄, PGE₂, cyclooxygenase-2 (COX2), and TXB₂ have been studied *in vitro* and have been noted to cause melanocyte enlargement and dendritic proliferation, suggesting melanocyte activation.^{5,8–12} Other cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF α), membrane-type stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), epidermal growth factor, and reactive oxygen species, such as nitric oxide, also stimulate melanocytes to increase melanin synthesis and transfer pigment to surrounding keratinocytes.^{8,9} SCF has been shown to stimulate proliferation of human melanocytes in culture and xenografts of human skin.^{7,13} In addition, UVB radiation from sunlight increases gene expression of basic fibroblast growth factor (bFGF), IL-1, and endothelin-1 (ET-1), which increases gene expression of tyrosinase, directly stimulating synthesis of melanin biopolymers.^{6,7,14,15} After exposure to ultraviolet A (UVA), human keratinocytes in a conditioned medium have increased levels of IL-6, interleukin-8 (IL-8), and GM-CSF.⁷

Dermal hypermelanosis can occur when inflammation disrupts the basal cell layer of the epidermis, causing melanin to be released from the keratinocytes of the epidermis and become phagocytosed by dermal papillary macrophages in a process known as pigmentary incontinence.^{8,16} Dermal hypermelanosis can also occur as a result of abnormal migration and differentiation of melanoblasts manifesting as ectopic melanocytes in the dermis. This clinically manifests as a Mongolian spot, nevus of Ito, nevus of Ota, or nevus of Hori based on the anatomical location.^{2,16}

Melanin is derived from the hydroxylation of the amino acid L-tyrosine or L-phenylalanine via the key rate-limiting enzyme tyrosinase. Tyrosine is metabolized into two types of melanin: eumelanin (brown-black melanin) or pheomelanin (yellow-red melanin). Increased tyrosinase activity leads to increased eumelanin production, whereas decreased tyrosinase activity leads to the default synthesis of pheomelanin.^{6,17,18}

Several signaling pathways have been found to play a role in the synthesis, differentiation, and survival of melanocytes. Microphthalmia-associated transcription factor (MITF) is a key transcription factor in upregulating the expression of tyrosinase and stimulating melanogenesis.^{19,20} It also aids in the transport of melanosomes to the dendritic tips in preparation for transfer to keratinocytes.²¹ The expression of MITF is mainly controlled

by the MSH/cAMP and KIT signaling pathways. α -MSH and adrenocorticotrophic hormone (ACTH) bind to the melanocortin-1 receptor (MC1R) on the surface of melanocytes. Activated MC1R in turn activates adenylate cyclase via G protein-coupled activation, increasing intracellular cAMP levels and cAMP-responsive element-binding protein (CREB) transcription factor family members. CREB, along with other key transcription factors, including SOX10 and PAX3, is responsible for upregulation of MITF expression.^{6,22} Of note, α -MSH also increases melanin biosynthesis directly by removing a tyrosinase inhibitor.⁶ When combined with UV radiation, α -MSH has been shown to have a potentiating effect on melanogenesis.²

The loss of *protein kinase cAMP-dependent type I regulatory subunit alpha* (PRKAR1A) gene function in Carney complex results in increased cAMP activity. This is thought to play a role in the production of lentigines, ephelides, blue nevi, and CALMs that are characteristic of this rare autosomal dominant inherited disorder.^{3,23} The large CALMs that develop in McCune–Albright syndrome are also thought to be due to hyperactivation of the cAMP pathway.^{3,24} Increased ACTH in multiple endocrine disorders, including Addison's disease, Cushing's syndrome, and hyperthyroidism, results in increased stimulation of MC1R, which increases melanin synthesis and causes hyperpigmentation. The exact etiology of melasma is unknown, but reports show that α -MSH is elevated in lesional skin compared with perilesional skin.^{3,25}

The KIT signaling pathway also stimulates MITF, but it does so by activating the Ras–mitogen-activated protein kinase (MAPK) pathway. SCF binds to the c-KIT receptor on the surface of melanocytes and triggers phosphorylation of tyrosine. This triggers multiple intracellular signaling cascades that eventually activate the Ras–MAPK pathway and upregulate MITF expression. The deregulation of the KIT pathway and overexpression of KIT ligand (KITL) is thought to play a role in the development of familial progressive hyperpigmentation.³

The Wnt signaling pathway primarily plays a role in embryogenesis and cancer development. Wnt proteins bind to the frizzled family cell surface receptors and prevent a multiprotein complex from degrading β -catenin. β -Catenin plays a crucial role in the development of mature melanocytes during embryogenesis.³ In addition, melasma-affected skin has been found to decrease expression of WIF-1, a Wnt antagonist, which results in increased Wnt expression and melanogenesis.²⁶

More than 150 genetic alleles are involved in coding for skin pigmentation and its related pathways.²⁷ Hyperpigmented lesions in dyschromatosis symmetrica hereditaria (reticulate acropigmentation of Dohi), incontinentia pigmenti, linear and whorled nevoid hypermelanosis, and neurofibromatosis type I are due to gene defects affecting early melanocyte development and function. The reticular hyperpigmentation seen in Dowling–Degos syndrome and Naegeli–Franceschetti–Jadassohn syndrome is due to defects in keratin genes, which are involved in

cell structure and metabolism. The lentigines of multiple lentigines syndrome and Peutz–Jeghers syndrome are a result of dysregulation of the Ras pathway. The hyperpigmentation of dyskeratosis congenita and xeroderma pigmentosum is due to gene defects involved in DNA repair.

Hyperpigmentation can also be caused by deposition of other endogenous and exogenous pigments. Hemosiderin deposition, as a result of recurrent extravasation of red blood cells in the dermis, can be seen in numerous skin conditions, including chronic venous insufficiency, capillaritis, hemorrhagic disease, and hemochromatosis. This commonly manifests clinically as a red-brown discoloration of the skin. Iron and other heavy metals, including silver, gold, and mercury, can mimic dermal hypermelanosis, and some metals, such as iron, may stimulate melanogenesis. Studies have shown that skin biopsies of the classic gray to bronze hyperpigmentation in patients with hemochromatosis reveal dermal iron deposition and increased epidermal melanin in the basal cell layer.^{28,29} Ochronosis, also known as alkaptonuria, is an autosomal recessive disorder that causes a blue-black discoloration of cartilage, skin, and other connective tissues. It is due to a defect in homogentisic acid oxidase, which causes an accumulation of homogentisic acid systemically.^{26,30} Exogenous ochronosis is also caused by an accumulation of homogentisic acid but is confined to the skin, as it is thought to be due to topical medications, including hydroquinone and phenols.³¹ Numerous other medications can induce hyperpigmentation, but the clinical patterns can vary greatly based on the offending drug. The most commonly implicated drugs include tetracyclines, antimalarial agents (including chloroquine and hydroxychloroquine), amiodarone, and multiple antipsychotic and cytotoxic agents.³²

Hyperpigmentation is a result of the complex interplay of a variety of cell signals that alter gene expression. The majority of hyperpigmentary disorders do not carry a mutation in the key genes involved in melanogenesis, but rather are due to multiple stimulatory signals triggering increased melanin production.³³ There is still much to learn about the exact pathogenesis of many of the more common causes of hyperpigmentation, including post-inflammatory hyperpigmentation and melasma. As the mechanisms surrounding hyperpigmentary disorders are better elucidated, the possibility of new, targeted therapies arises.

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Disorders of Hyperpigmentation

INTRODUCTION

Melasma belongs to the acquired hyperpigmentation skin diseases. It is a common dyschromia located on sun-exposed areas, mainly on the face and occasionally on the neck and forearms.¹ The term *melasma* means “black,” and it originates from the Greek word *melas*. The incidence of melasma is dependent on solar radiation, population ethnicity, and skin phototype; it is more common in tropical regions, in Hispanic, Asiatic, Mediterranean African, and Middle Eastern populations. Melasma usually affects more pigmented skin phenotypes, such as skin types IV–VI. Also, it affects women more commonly, with a female-to-male ratio of 9 to 1.^{1,2} In Southeast Asia, the prevalence of melasma was reported to be 40% in adult women and 20% in adult men.³

PATHOGENESIS

Skin color is determined mainly by the quantity, type, and distribution of melanin within the skin. The synthesis of melanin is a complex multistep process catalyzed by various enzymes, mainly tyrosinase.⁴ Melasma is due to the increased focal epidermal activity of melanocytes producing melanin,⁵ and microscopically there is increased melanin in epidermal keratinocytes and/or dermal macrophages.⁶ What causes the activation of melanocytes in melasma is not clear. Ultraviolet (UV) sun exposure, genetic predisposition, photosensitizing medicines, and hormones (pregnancy and oral contraceptives) are established aggravating factors in melasma.⁷ Genetic predisposition is one of the main causes of melasma development, as indicated by the racial differences and positive family history in melasma.⁶ UV irradiation stimulates melanogenesis by direct effects on melanocytes (1,2-diacylglycerol formation and nitric oxide [NO] production), as well as indirect effects on keratinocytes releasing melanogenic factors, such as basic fibroblast growth factor (bFGF), nerve growth factor (NGF), endothelin-1 (ET-1), melanocyte-stimulating hormone (MSH), adrenocorticotrophic hormone (ACTH), and NO.⁶

An increased melanin amount in the epidermis and an increased staining intensity and number of epidermal melanocytes have been found in biopsies of melasma lesions compared with adjacent normal skin.⁸ It has been shown that there are higher levels of melanin and proteins associated with melanogenesis, such as tyrosinase-related protein-1 (TYRP1) mRNA expressed in melasma skin lesions compared with perilesional normal skin.⁹ Also, basal keratinocytes from facial melasma in 14 women displayed changes in nuclear form and chromatin texture.⁵ High epithelial expression of melanocortin-1 receptor

(MC1R), α -MSH, estrogen, and progesterone receptors have been described in melasma.^{10,11} Apart from increased pigmentation, it has been shown that melasma lesions also have more elastosis and vascularization than perilesional skin.^{8,12,13}

Melasma occurs in 14.5%–56% of pregnant women and in 11.3%–46% of those using oral contraceptives in various countries, delineating the role of female sex hormones (mainly estrogens and, to a lesser extent, progesterones) as a precipitating factor for melasma.^{6,14–16} An increase in male melasma has been linked to the use of the anti-androgen finasteride in one male patient.¹⁷ Additional risk factors for the development of melasma reported in an age-matched case-control study in 414 adult women with facial melasma in Brazil included darker phototypes (phototypes III–V), sun exposure, regular antidepressant or anchiolytic use, menstrual irregularity, pregnancy history, and a family history of melasma. The higher risk was described in individuals with a positive family history that had a 10-fold increased risk for melasma.² A survey by a self-administered questionnaire of 324 women treated for melasma reported that the mean age of melasma onset was 34 years, and 48% had at least one relative with melasma. The most common time of onset was after pregnancy (42%), often years after the last pregnancy, with 29% appearing prepregnancy and 26% during pregnancy.¹⁸

Moreover, altered dermal vasculature has been implicated in melasma pathogenesis, and pigmented melasma lesions showed an increased number of dermal blood vessels and vascular endothelial growth factor (VEGF) expression.¹²

CLINICAL PRESENTATION

Melasma presents as irregular, light to dark brown, grey, blue, or black macules and plaques, mainly on the face, and also on the neck, V area of the chest, and rarely the upper extremities. Mucosae are not affected.⁷

Melasma of the face is classified into three clinical types based on its location:^{7,19}

1. The centrofacial pattern. This is the most common pattern. It involves the forehead, cheeks, upper lip, nose, and chin (Figure 5.1).
2. The malar pattern. This involves the cheeks and nose (Figure 5.2).
3. The mandibular pattern. This involves the ramus of the mandible.

The location of the melanin pigment in the epidermis and/or dermis can be evaluated with Wood's light and may impact the treatment decision.²⁰ Dermal melasma is



(a)



(b)



(c)

Figure 5.1 (a–c) Centrifacial type of melasma: irregular brown patches involving the forehead, the nose, and the upper lip.

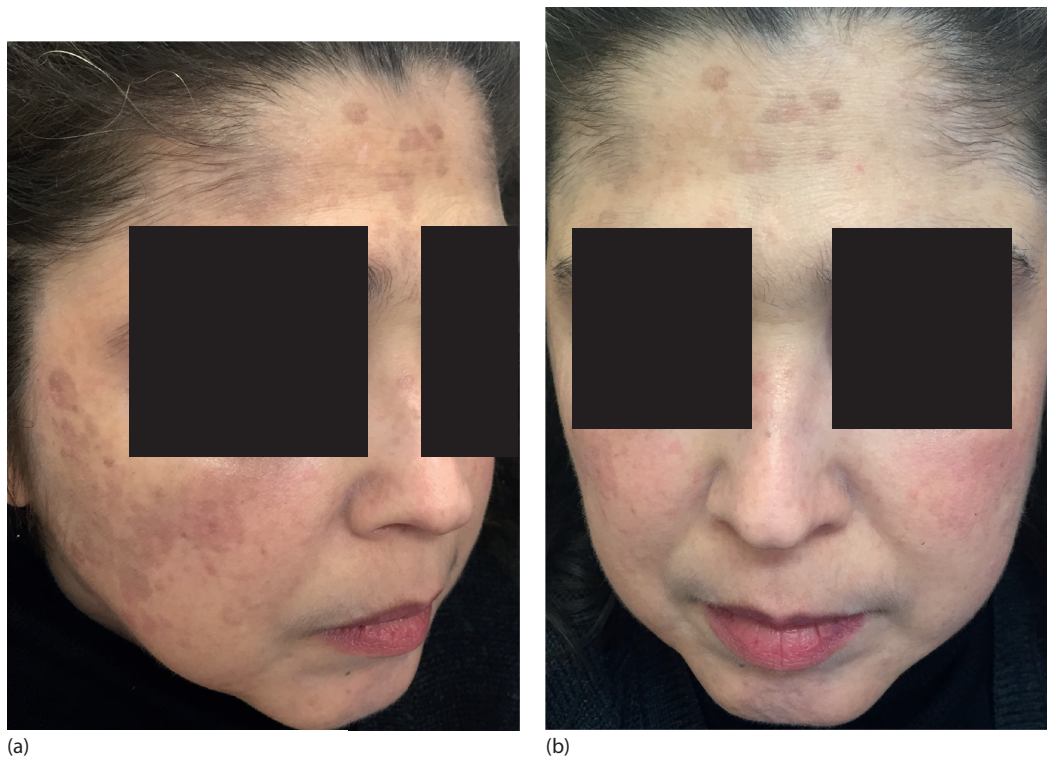


Figure 5.2 (a and b) Malar type of melasma: brown-gray macules mainly located on the malar areas, but also on the forehead.

unresponsive to treatment, partially because most therapies do not target the resident macrophages in the dermis that phagocytose melanin.²¹

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of melasma is made clinically. Laboratory examinations and biopsy are required only in the case of an uncertain diagnosis to exclude other hyperpigmentary diseases. The most common hyperpigmentation disorders are postinflammatory hyperpigmentation (PIH) and lentigines. Of note, these hyperpigmentations may coexist in the same patient.⁶ PIH occurs on the site of preceding inflammation or preexisting skin lesions, without specific site predilection.⁶

TREATMENTS FOR MELASMA

Melasma may cause a significant negative impact on the patients' psychology and quality of life. Treatments for melasma can be categorized as topical bleaching agents, lasers, and other treatments, including chemical peeling and experimental therapies. The key principles of therapy include the inhibition of the activity of melanocytes, the inhibition of the synthesis of melanin, the removal of melanin, and the disruption of melanin granules.⁷

A 2014 systematic review reported a lack of standardized outcome, short duration, and poor methodology in studies of melasma treatments. This review included 20 studies with a total of 2125 participants covering 23 different treatments and reported that the triple-combination cream (hydroquinone [HQ], tretinoin [TR],

and fluocinolone acetonide [FA]) was more effective at lightening melasma than HQ alone (relative risk 1.58, 95% confidence interval 1.26–1.97) or any of the agents in a dual-combination cream. Azelaic acid (20%) was significantly more effective than 2% HQ (relative risk 1.25, 95% confidence interval 1.06–1.48) for lightening melasma. No studies provided long-term data or quality of life results.²²

GENERAL MEASURES AND SUN PROTECTION

The successful management of melasma relies on highlighting the importance of avoiding precipitating exogenous factors. UV and visible light can initiate or aggravate melasma. So, regular use of broad-spectrum (ultraviolet A and ultraviolet B) sunscreens is necessary both for preventing melasma and for enhancing the effectiveness of topical therapies.²³ The use of a UV broad-spectrum sunscreen that contained a visible light-absorbing substance (iron oxide) resulted in greater improvement in melasma (Melasma Area and Severity Index [MASI] scores) than UV-only broad-spectrum sunscreens in a study of 68 female Latin American patients.²⁴ Also, a randomized controlled trial in 40 melasma patients showed that the application of a sunscreen that contained filters against both UV and visible light (iron oxides) resulted in the prevention of melasma, with a lower increase in the MASI score during the summer, compared with a sunscreen against only the UV spectrum.²⁵ Women with melasma receiving oral contraceptives should discontinue them and choose another method of contraception if possible.

However, melasma may persist despite oral contraceptive discontinuation.²⁶

TOPICAL BLEACHING AGENTS

Various topical bleaching treatments have been used for melasma. These include HQ, nonphenolic compounds (kojic acid, azelaic acid, and TR), and combination formulas.⁷

Hydroquinone

HQ is a well-known bleaching agent. It inhibits tyrosinase activity, and therefore inhibits the conversion of tyrosine to melanin, and it increases the degradation of melanosomes. It is active only in epidermal melanocytes that have active tyrosinase activity, while it is inactive for dermal melanophages.^{7,27}

The efficacy of HQ is related to its concentration, the vehicle used, and chemical stability. The use of 3%–5% HQ is recommended for melasma treatment, and lower concentrations of 2% are used as maintenance therapy.²⁸

HQ side effects are dose related, and they are associated with the concentration used and the duration of application. They include irritant or allergic contact dermatitis, nail discoloration, guttate hypomelanosis, and exogenous ochronosis. HQ is contraindicated during pregnancy and lactation. In the European Union, HQ has been banned from use as a cosmetic ingredient since 2001 for concerns such as ochronosis and occupational vitiligo. However, it is still available as prescription medication.²⁹

Nonphenolic compounds

Kojic acid is a fungal metabolic product (*Aspergillus* and *Penicillium*). It inhibits tyrosinase activity. It may cause sensitization and allergic contact dermatitis.³⁰ Sun exposure should be avoided during use of kojic acid. It may be used alone at a concentration of 1%–4% twice daily or as combination treatment together with 5% glycolic acid.^{31,32}

Azelaic acid is a dicarboxyl acid derived from *Pityrosporum ovale*. It inhibits tyrosinase in hyperactive melanocytes and has anti-inflammatory action. It is an off-label treatment for melasma. Twice daily, long-term application is needed, often more than 3 months. It is very well tolerated.³³

TR (retinoic acid) is the most commonly used topical retinoid for the treatment of melasma. It acts by removing melanin via keratinocyte shedding, enhances the penetration of HQ, and prevents the oxidation of HQ.³⁴ TR may result in erythema and scaling. Patients should be advised to avoid sun exposure and apply sunscreens.⁷

Combination formulas

The desired bleaching effect may be enhanced with combination formulas that contain two or three bleaching agents. Combination therapy aims to increase efficacy, minimize side effects, and shorten the duration of treatment.

A well-known combination formula with HQ, TR, and a topical corticosteroid is the Kligman–Willis formula: 5% HQ, 0.1% TR, and 0.1% dexamethasone in ethanol and 1:1

Table 5.1 Modification combination formula proposed by Katsambas and Antoniou.

Ingredients	Concentrations
Hydroquinone	4%–5%
Tretinoin	0.025%–0.05%
Hydrocortisone	1%
Sodium bisulfate	0.1%
or ascorbic acid	0.1%
In ethanol and propylene glycol	
1:1 or in a hydrophilic ointment	

Table 5.2 Triple-combination cream.

Ingredients	Concentrations
Hydroquinone	4%
Tretinoin	0.05%
Fluocinolone acetonide	0.01%
In an hydrophilic cream as vehicle	

propylene glycol or in hydrophilic ointment. Application for 5–7 weeks is recommended.³⁵

A modified formula proposed by Katsambas and Antoniou contains 4% HQ, 0.05% TR, and 1% hydrocortisone acetate in ethanol and 1:1 propylene glycol or in hydrophilic ointment. In this formula, the concentration of TR is 0.05% and 1% hydrocortisone acetate is used instead of dexamethasone. By lowering the concentration of TR and the use of a nonfluorinated steroid, the aim is to minimize the irritation caused by TR and eliminate local steroid side effects. The above formulation is applied twice a day until improvement, with a maximum duration of 8–10 weeks (Table 5.1).³⁶ A further modification is the selection of FA as a low-potency topical corticosteroid (Table 5.2). This treatment is the first triple topical treatment that has been approved by the U.S. Food and Drug Administration (FDA) for the short-term (8-week) treatment of moderate to severe facial melasma.^{37–39}

LASERS AND OTHER THERAPIES

Fractional laser therapy is the only laser treatment for melasma that has been approved by the U.S. FDA, and it could be used as a third-line treatment in severe cases that have not responded to other treatments and are willing to accept a risk for postprocedure hyperpigmentation.⁴⁰

The rationale for use of vascular lasers (pulsed dye laser or copper bromide laser) for melasma was based on the observation of increased vascularization in melasma lesions, but they have shown mixed and controversial results.^{41,42}

Chemical peelings remove excess melanin. Superficial peels may be used for melasma in fair-skinned patients. On the other hand, peels should not be used for darker skin types, as they are associated with the risk of PIH and aggravation of melasma.⁴³ Maintenance therapy with 2% HQ is recommended.

EXPERIMENTAL THERAPIES (TABLE 5.3)

Tranexamic acid is a plasmin inhibitor that can prevent UV-induced pigmentation in pigs and decreases melanocyte tyrosinase activity *in vitro*. In an open-label trial in 35 melasma patients (of whom 33 were women) with oral tranexamic acid three times daily, all patients showed improvement at 16 weeks.⁴⁴

Undecylenoyl phenylalanine is a novel skin-lightening agent, probably acting as an α -MSH and beta-adrenergic receptor (β -ADR) antagonist. A double-blind vehicle-controlled study of 2% topical undecylenoyl phenylalanine has been conducted in 40 females with melasma. Of the 20 patients treated with the active treatment, 17 (85%) showed a partial response. The reported side effects were minor and included erythema, itching, or burning at the site of application.⁴⁵

Ten percent zinc sulfate was compared with 4% HQ solution once daily for 2 months in 93 women with melasma. Topical zinc was not very effective, as it resulted in a smaller decrease in the MASI score than HQ (18.5 vs. 43.5, respectively, $p < 0.001$).⁴⁶

Lignin peroxidase is an enzyme derived from the tree fungus *Phanerochaete chrysosporium* that may break down melanin. Lignin peroxidase in a cosmetic lotion formulation was investigated in a randomized controlled, split-face trial in 60 female patients with mild to moderate facial dyspigmentation. This preparation was applied twice daily for 12 weeks and resulted in similar skin lightening as 4% HQ with no adverse events or tolerability issues noted.⁴⁷

A systematic review investigated clinical studies on the effects of plant extracts, herbal preparations, and isolated plant-derived compounds for hyperpigmentation disorders.⁴⁸ Botanical therapies included topical, oral, adjunctive, and preventative treatments. Oral therapies included procyanidin, pycnogenol (standardized extract of French maritime pine bark), *Polypodium leucotomos* extract, and Chinese herbs. Botanicals (with active compounds such as alpha-arbutin, alpha-bisabolol, flavonoids, or polyphenols) may inhibit hyperpigmentation via inhibition of tyrosinase, or anti-inflammatory and antioxidant effects. Also, botanicals (soy extract and oral proanthocyanidin) may be used as preventative agents. Botanicals cause less irritation than conventional therapies for melasma; however, plant-based therapies are known to cause allergic reactions and phototoxic reactions, while infrequent serious adverse events are possible, especially with oral and high-concentration formulations. The authors concluded that existing studies show that botanical therapies for the treatment of hyperpigmentation are promising, although more

rigorous clinical studies are needed. Limitations for the clinical studies on botanicals for melasma include inconsistencies in study methodology and botanical extraction method and inadequate control for confounding variables, such as sun exposure and sunscreen use.⁴⁸

MAINTENANCE TREATMENT FOR MELASMA

Since melasma is a persistent skin disease and it commonly relapses after improvement, maintenance therapy may be useful. A study in 70 patients evaluated the application of the triple-combination cream once daily for 12 weeks or until clearance, followed by a regimen of application twice weekly for a total maximum of 24 weeks. Relapses were seen in most of the patients that followed the twice weekly regimen, and the reinitiation of daily application was necessary.⁴⁹

In conclusion, the management of melasma is a multistep process that requires the avoidance of precipitating factors, active treatment with topical bleaching agents, and a maintenance regimen. Also, chemical peels, lasers, and light sources have been used for treating melasma. The choice of treatment should be tailored to each patient's needs, and an important challenge with melasma treatment is the fact that it commonly relapses after treatment.

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Table 5.3 Experimental therapies for melasma.

- Tranexamic acid
- Undecylenoyl phenylalanine
- 10% zinc sulfate
- Lignin peroxidase
- Botanical agents

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Erythema dyschromicum perstans

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INTRODUCTION

Erythema dyschromicum perstans (EDP) (also known as ashy dermatosis, dermatosis cenicienta, or erythema chronicum figuratum melanodermicum) is a rare, chronic, benign skin disorder belonging to the group of idiopathic acquired hypermelanoses.

HISTORY

EDP was initially described in El Salvador by Oswaldo Ramirez in 1957. He referred to the patients with EDP as *los cenicientos*, which is the Spanish term for the “ashen ones.” The Spanish term *cenicienta* also means Cinderella, a folklore character closely associated with ashes due to sitting alone by the fireplace.¹

The term *erythema dyschromicum perstans* was credited to Marion Sulzberger, and it was initially used in Venezuela in 1961. This term aimed to describe the red borders of the active lesions and the dyschromias of the persistent lesions.²

EPIDEMIOLOGY

About 300 cases of EDP have been published in the English-language literature.³ This skin disorder seems to be more prevalent in Central and South America and in Asian populations. However, EDP has also been reported from several other parts of the world.^{1,4}

EDP tends to affect darker-skinned individuals, particularly those of Hispanic decent, but cases with Caucasian, Indian, and African American patients have also been described. Regarding prepubertal children, the majority of patients are Caucasians.⁵ A possible explanation may be the underreporting of Hispanic children patients or the origin of literature from areas with a Caucasian population.⁶

Although a higher frequency of EDP has been reported in females, there exists no clear sexual predilection.^{1,7}

The age range that can be affected is broad.⁸ However, the majority of patients are younger than 30 years old, while it is estimated that approximately 8% of the total patients with EDP are of prepubertal age.⁵

PATHOPHYSIOLOGY

The underlying pathophysiology of EDP, as well as its exact etiology, remains obscure. Many authors consider EDP as a variant of lichen planus or lichen planus actinicus.^{9–11} A wide spectrum of predisposing factors has been mentioned, as well as mediation of the immune system and genetic predisposition. Despite that, in the great majority of patients, and especially in pediatric ones, the trigger factor cannot be identified.¹²

Associations with ammonium nitrate, an intestinal parasite infection by nematodes, orally administered radiographic contrast media (barium sulfate), cobalt allergy, chlorothalonil exposure among banana farm workers, atopy, dyslipidemia, endocrinopathy (hypothyroidism and diabetes mellitus), and chronic hepatitis C infection have been found.^{8,13–15} Regarding the geographical distribution of EDP, it has been suggested that environmental contaminants and pollutants may be responsible. Drugs, including oral antibiotics, and particularly penicillin, ethambutol, and benzodiazepines, have also been implicated.^{16–19}

Impairment of the immune system may play a role in the pathogenesis of EDP. Two cases of HIV-seropositive patients affected by EDP have been reported.^{16,20}

Regarding the gene frequencies of the HLA-DR alleles in Mexican patients, the most frequent allele was HLA-DR4, while the most frequent molecular subtype was DRB1*0407.²¹

CLINICAL PRESENTATION

EDP is a pigmentary disorder with insidious onset and slow progression.⁶ The clinical course may differ between adults and children patients. EDP may persist in adults, and it is unlikely to resolve spontaneously, while in the majority of children (~70%), it may resolve within 2–3 years.^{5,6}

EDP presents clinically as slate-gray to blue-brown, hyperpigmented macules and patches (Figure 6.1). Their shape is oval, circular, or irregular. The eruption may follow the skin cleavage lines. The size of the lesions usually varies between 0.5 and 2.5 cm, or they can be even larger.^{5,22}

In the early stages of the disease, the macules may be surrounded by erythematous, elevated, nondesquamative borders measuring 1–2 mm in width, which eventually fade after months. Although this feature is uncommon, it is unique for EDP.¹² In the late stages, the macules turn gray-blue with ill-defined margins.²³

The macules slowly extend peripherally or multiply, affecting extensive anatomic areas. The eruption is located at the trunk, proximal aspects of the extremities, face, and neck, and it is symmetrically distributed. The lesions are usually asymptomatic; mild pruritus may occur occasionally.¹² The mucosal membranes, palms, soles, scalp, and nails are not involved.²⁴

HISTOLOGY

The histological findings of EDP are not pathognomonic. The biopsy specimen is obtained in order to exclude other



Figure 6.1 Hyperpigmented macules and patches in EDP.

possible diagnoses. If active macules are present, the biopsy sample should be obtained from the borders of the lesions.

The histological pattern differs between the early and late phases of the eruption. Active lesions show hyperkeratosis, a thinned epidermis, and mild vacuolar degeneration at the basal cell layer. Mild lichenoid infiltrate by lymphocytes and histiocytes and incontinence of melanin pigment with increased melanophages at the upper dermis can also be observed. Colloid bodies are occasionally identified. The predominant characteristic of residual macules is melanin incontinence. Epidermal atrophy and elimination of rete ridges can be seen, while the grade of basilar vacuolar degeneration and cell infiltrate may vary from slight to extensive.^{25,26}

Positive immunoglobulin M (IgM), IgG, fibrinogen, and C3 staining of colloid bodies have been observed at differential interference contrast (DIF) microscopy in active lesions, while direct immunofluorescence has demonstrated positive staining for fibrinogen at the dermoepidermal junction.²⁷

Dermal infiltration by both CD4+ and CD8+ T cells, intense OKT 4 and OKT 6 staining of Langerhans cells, and immune-associated antigen expression in keratinocytes are identified in immunopathologic studies of EDP.²⁸

LABORATORY FINDINGS

There is no specific laboratory examination or imaging technique for establishing of the diagnosis of EDP.

Positive patch tests have been reported in 40% of the patients, indicating that contact allergens may play a role in the pathogenesis of EDP, as previously mentioned.²⁹

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for EDP includes the following:

- **Lichen planus pigmentosus:** The eruption consists of pruritic, irregular or oval, brown to gray-brown macules and patches on the forehead, temples, and flexor folds and characterized by recurrences and remissions.

Mucosal membranes can be involved. Early lesions are not surrounded by erythematous borders. A histological image demonstrates melanophages, perivascular mononuclear cell infiltrate in the upper dermis, and vacuolization of the basal layer. However, Max Joseph spaces, which are not present in EDP, can be identified in some, but not all, cases of lichen planus pigmentosus.^{25,29}

- **Postinflammatory hyperpigmentation:** This is secondary to lichenoid drug eruption, pityriasis rosea, small plaque parapsoriasis, lichen planus, erythema multiforme, or reticulated papillomatosis of Gougerot and Carteaud.²³
- **Generalized fixed drug eruption:** There is a history of drug intake. Regarding histological examination, intense basal hydropic degeneration, dyskeratotic keratinocytes, and eosinophilic infiltrate are observed.^{5,30}
- **Pigmented contact dermatitis:** It presents with erythema, papules, swelling, and itching. The main histological features are the liquefaction of basal cells and the presence of melanophages.²⁹
- **Pinta:** The serological examination for syphilis is positive.²³
- **Idiopathic eruptive macular pigmentation:** Its clinical presentation consists of brownish, nonconfluent macules without erythematous borders. Histologically, it shows plenty of mature melanosome macrophages and keratinocytes at the basal layer that contain clustered melanosomes.³¹
- **Cutaneous manifestations of Addison's disease and hemochromatosis.**²³
- **Other dermatologic disorders, including lichenoid drug reaction, leprosy, argyria, melasma, macular amyloidosis, macular urticaria pigmentosa, and poikiloderma vasculare atrophicans.**^{8,12}

TREATMENT

Treatment of EDP is challenging. There is yet no standard therapy, while therapeutic results are not satisfactory. Suggested treatments include dapsone, clofazimine, topical tacrolimus, and ultraviolet phototherapy. Other treatment options are systemic and topical corticosteroids, antibiotics, retinoids, vitamin A, vitamin C, griseofulvin, isoniazid, chloroquine, keratolytic agents, chemical peels, and sun protection.^{5,12,23,32–35}

Dapsone was administered to three patients at a dose of 100 mg daily for 2–3 months, and it was reported to be effective.^{23,32}

In a study by Piquero-Martín et al., seven out of eight patients responded to clofazimine. Clofazimine was administered at a dose of 100 mg daily for those weighing more than 100 kg and 100 mg every other day for patients less than 40 kg for 3 months, followed by reduction to 400 mg weekly and 200 mg weekly, respectively.³³ Regarding its action in EDP, clofazimine eliminated the expression of intercellular molecule 1 and HLA-DR and diminished the infiltrate by mononuclear cells.³⁴

Two patients with EDP responded to application of 0.1% topical tacrolimus ointment twice daily for 2–3 months. No recurrence was reported during the follow-up.³⁵

Narrowband ultraviolet B phototherapy has been found to be effective in one patient with EDP. Ultraviolet phototherapy is suggested to act in two ways. First, it induces hyperpigmentation of the normal skin by stimulating pigment production. Second, it suppresses the function of the immune system. Ultraviolet phototherapy enhances the thickening of the stratum corneum and apoptosis of T lymphocytes, resulting in reduction of the infiltrate of inflammatory cells.¹²

In a study of 14 children conducted by Torrelo et al., no medical treatment was recommended. Parents and children should be informed that EDP is mainly a cosmetic issue, and in children it may resolve in a few years.⁶ In order to avoid hyperpigmentation of the lesions, sun protection is required.⁵

Corrective camouflage, such as camouflage creams and makeups, can be applied in order to cover up the lesions.¹²

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Lichen planus pigmentosus

EFSTRATIOS VAKIRLIS and DIMITRIOS IOANNIDES

INTRODUCTION

Lichen planus pigmentosus (LPP) was first described by Bhutani et al. in 1974.¹ The authors considered LPP a rare macular variant of lichen planus (LP) in dark-skinned individuals based on the histologic resemblance between the two entities and the coexistence of lesions of LPP with other forms of LP in about 30% of the cases.²

Erythema dyschromicum perstans (EDP), also known as ashy dermatosis, was first described by Ramirez in El Salvador in 1957.³ It is an acquired slowly progressive dermal hyperpigmentation of unknown etiology most prevalent in Latin America but reported from most areas of the world. It is characterized by ash-colored or brown macules and patches of varying size, most commonly on the trunk and the proximal extremities.^{3–6}

Most clinicians regard the terms as synonymous and use them interchangeably.

Some authors support the opinion that LPP and EDP are possibly the same condition.^{2,5} Both entities affect young adults with dark phototypes, may coexist with LP, resemble each other clinically, and are histologically indistinguishable.^{5–7}

However, distinct clinical features have been emphasized by others. They highlight the presence of an elevated erythematous border around the lesions in the active phase of evolution, the absence of pruritus, and the predilection for the trunk as diagnostic clues for EDP.^{8–10}

Our concept is that all the aforementioned entities belong to the same phenotypic spectrum of dermal pigmentary disorders that result from basal layer damage and keratinocyte apoptosis due to lichenoid inflammation elicited by an unknown antigen.

EPIDEMIOLOGY

LPP is a rare entity most frequently described in India, Latin America, the Middle East, Korea, Japan, and the Mediterranean region.^{8,11,12} Dark-skinned individuals (Fitzpatrick's phototypes III–V) are more commonly affected. No clear sex predilection exists. LPP has its onset usually during the third or fourth decade of life. Numerous pediatric cases have been described.^{14–16}

ETIOLOGY: PATHOGENESIS

The nature of this disorder remains enigmatic. However, a number of etiological factors, like ingestion of ammonium nitrate, nematode infestation, radiographic contrast media, cobalt allergy, contact allergens, and chlorothalonil exposure among banana farm workers, have been implicated.^{13,17–21}

Retrospective studies incriminated mustard oil and amla oils, substances commonly used in India as potential etiological factors.¹⁸

LPP has been also described in patients with hepatitis C virus (HCV) or HIV infection.^{12,13,22–23} In a study, genetic susceptibility associated with HLA-DR4 has been found in Mexican Mestizo patients.²⁴ Three cases of EDP induced by omeprazole have been recently reported.²⁵ A case of LPP and Bazex acrokeratosis due to head and neck cancer with spontaneous resolution after the treatment of the malignancy has been reported.²⁶

The pathogenesis of LPP is poorly understood, although it appears to involve a T-cell-mediated reaction to a yet unknown antigenic trigger in a genetically predisposed host. Antigen presentation is followed by activation of T cell. Activated cytotoxic T cells cause basal layer damage, keratinocyte apoptosis, and subsequent pigment incontinence.²⁷

CLINICAL MANIFESTATION

LPP is characterized by insidious onset. Most patients cannot recall the date of onset. However, cases with abrupt onset have been reported. LPP presents with ashen-gray (Figure 7.1), dark brown, or blue-brown macules or patches of varying size and shape, predominantly on sun-exposed areas (especially the forehead, temples, and neck) and flexural folds, including the axillary, inguinal, and inframammary regions. The term *lichen planus pigmentosus inversus* (LPPi) is used to describe patients with primary flexural involvement (Figure 7.2).^{28–34} The lesions are usually asymptomatic, although mild pruritus or burning sensation may be reported. The presence of pruritus varies among studies at between 27.3% and 62% of the patients.^{1,8,13}

The coexistence of LPP or EDP with LP, lichen planopilaris, Graham–Little–Piccardi–Lasseur syndrome, and frontal fibrosing alopecia (FFA) has been repeatedly reported. The LP lesions can accompany, precede, or follow the onset of LPP.^{35–38}

Mucosal involvement has been described in a minority of the cases.

Cases with the lesions in a unilateral linear, segmental, or Blaschkoid distribution have been reported.^{39–44}

Wood's light examination does not show accentuation of the pigmentation.

HISTOPATHOLOGY

Histologic examination may demonstrate a hyperkeratotic, relatively flat epidermis with loss of a rete pattern, vacuolization of the basal cell layer, occasional apoptotic



Figure 7.1 LPP presents with ashen-gray, dark brown, or blue-brown macules or patches of varying size and shape.



Figure 7.2 Lichen planus pigmentosus inversus.

cells (colloid bodies), a mild to moderate lymphohistiocytic perivascular infiltrate, and prominent pigment incontinence with melanophages in the dermis (Figure 7.3). Band-like infiltrate in the papillary dermis is found in a minority of the cases.^{1,8,11,13,45,46}

Immunopathologic studies have shown that immunoglobulin M (IgM), IgG, and complement staining colloid bodies increase the expression of adhesion molecules (ICAM-1 and LFA-1a) and HLA-DR molecules in epidermal keratinocytes, exocytosis of cutaneous lymphocyte antigen (CLA)-positive cells, and a dermal infiltration of T lymphocytes of both helper (CD4) and cytotoxic (CD8) phenotype. These findings are similar to those in LP.^{27,45,47}

DERMATOSCOPY

Dermatoscopic findings parallel those seen microscopically (Figure 7.4).

Blue-gray dots and globules seem to be the cardinal dermatoscopic findings reflecting the deposition of melanophages in the dermis.^{48–50}

In a dermatoscopic study of 255 LP lesions from 60 patients, which included 15 lesions of LPPI, the absence of Wickham striae and presence of pigment pattern were observed in all lesions.⁵⁰ Diffuse blue-gray dots and globules, diffuse peppering, annular perifollicular pigmentation, a linear pigmentation pattern, and cobblestone pigmentation were observed. The background color was found to be brown in all lesions. Different pigment patterns were observed in different lesions of the same patient at the same visit.⁵⁰

DIAGNOSIS

The diagnosis is based on a combination of clinical and histopathological features.

Al-Mutairi et al.¹³ proposed the clinical and diagnostic criteria as follows:

- Clinical presence of largely asymptomatic bluish- and blackish-brown, ill-defined macules, mainly on the face, neck, and upper extremities
- Histological
 - Epidermal changes: Basket-weave keratin layer, minimal change in epidermal thickness; keratinocyte apoptosis and vacuolar degeneration of the basal cell layer
 - Dermal changes: Presence of band-like or perivascular lymphohistiocytic infiltrates; scattered melanophages and melanin incontinence

We propose a modification of the aforementioned criteria based on the largest published histopathological study by Kanwar et al. in 2003.¹³

- Clinical presentation: Asymptomatic ashen-gray or dark brown macules and patches of various size and shape
- Distribution: Scalp, face, neck, proximal limbs, flexures
- Histological findings
 - Obligatory
 - Vacuolar degeneration of the basal layer or apoptotic keratinocyte

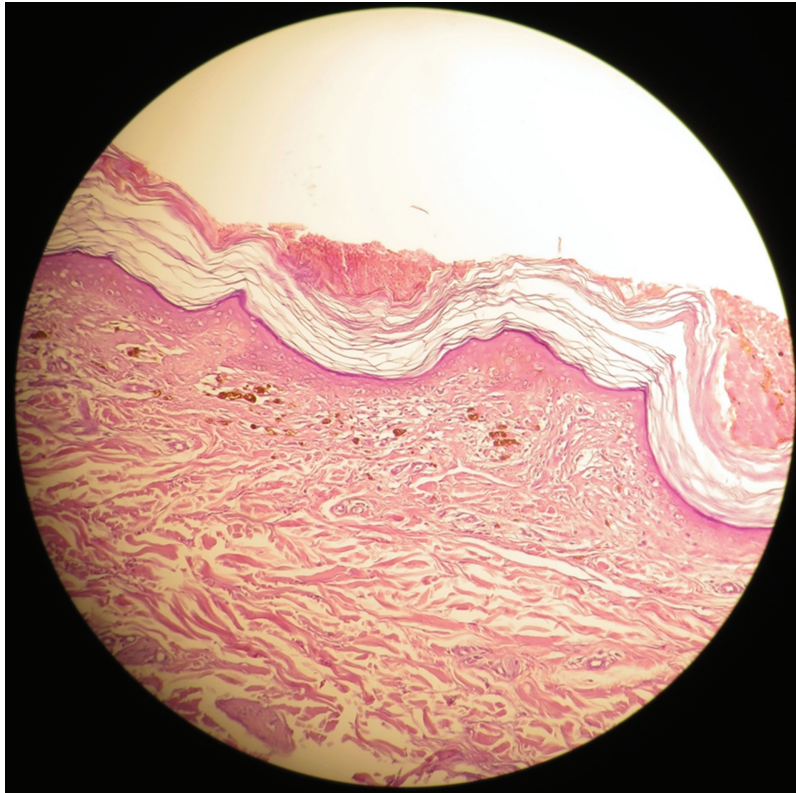


Figure 7.3 Histopathologic examination of LPP.

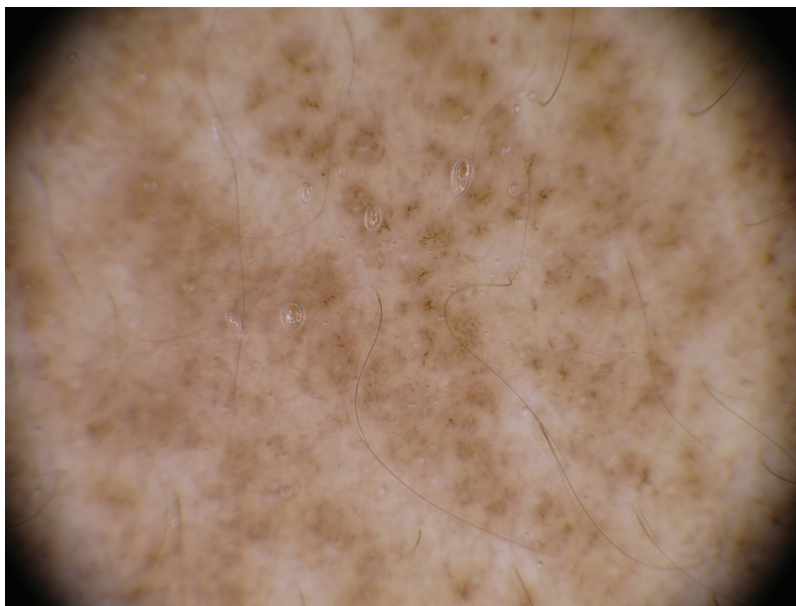


Figure 7.4 Dermatoscopic findings of LPP.

Table 7.1 Differential diagnoses of LPP and EDP.

Idiopathic eruptive macular pigmentation
Postinflammatory pigment alteration (PIPA)
Melasma
Macular amyloidosis
Urticaria pigmentosa
Fixed drug eruption
Addison's disease
Hemochromatosis
Incontinentia pigmenti (Bloch–Sulzberger syndrome)
Dowling–Degos disease
Acanthosis nigricans
Pigmented contact dermatitis (Riehl's melanosis)
Pinta
Lichenoid drug eruptions

- Melanophages in the dermis
- Perivascular lymphohistiocytic infiltrate
- Mandatory
 - Hyperkeratosis
 - Slightly atrophic and flattened epidermis
 - Band-like lichenoid infiltrate

DIFFERENTIAL DIAGNOSIS

The ash-gray to dark brown macules and patches of LPP should be distinguished from numerous acquired pigmentary disorders.^{51,52} Table 7.1 summarizes the main differential diagnosis.

THERAPY

The management of LPP remains challenging. No consistently effective treatment for this condition has been described. There are no prospective randomized controlled trials to guide the management of LPP.⁵³

Various treatments, such as sun protection, topical corticosteroids, hydroquinone, and chloroquine, have been used with little benefit.⁵⁴

Treatment with peeling agents is doomed to failure due to the dermal deposition of the pigment.

Several case reports have demonstrated a marked decrease in pigmentation on treatment with 100 mg/day dapsone. The duration of therapy ranged from 8 weeks to 3 months.^{55–57}

A prospective clinical and immunohistochemical study by Baranda et al. evaluated the effect of clofazimine therapy on the expression of adhesion and lymphocyte activation molecules in EDP in six patients. Four out of six patients experienced marked improvement after 3 months of therapy with 100 mg/day clofazimine. The authors detected clearance of these molecules after the 3-month therapy with clofazimine.⁵⁸

Topical tacrolimus seems to be a promising therapeutic choice. Al-Mutairi et al. observed significant clearance in 7 out of 13 patients with LPP treated with 0.03% tacrolimus for 16 weeks.¹³ Mahajan et al. reported successful

treatment with 0.1% topical tacrolimus ointment in two patients.⁵⁹

Treatment with low-fluence Q-switched neodymium yttrium aluminum garnet (QS Nd:YAG) laser therapy was successful in two patients with LPP, while a nonablative 1550 nm fractional laser was ineffective in eight patients.^{47,60,61}

PROGNOSIS

LPP in adults is characterized by insidious onset and chronic course and is unlikely to remit spontaneously. The prognosis in children is more favorable. Spontaneous resolution or improvement within 1–3 years was observed in 6 of 11 cases in a study of LPP in prepubertal children, leading to the conclusion that no treatment is a reasonable choice in the pediatric population.¹⁵

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INTRODUCTION

The term *amyloidosis* is used to define the abnormal extracellular deposition of insoluble polymeric protein fibrils that share characteristic staining properties in tissues and organs. The origin of amyloid is diverse; 16 different fibril proteins have been described. When amyloid deposition is restricted to a single tissue site, amyloidosis is classified as localized or organ limited. Primary localized cutaneous amyloidosis (PLCA) is characterized by amyloid deposition limited to previously apparently normal skin without systemic organ involvement. The best-recognized local forms of amyloidosis confined to the skin are the more commonly seen macular and lichen subtypes (Figures 8.1 through 8.3) and the rare nodular subtype.¹⁻⁴

ETIOLOGY: PATHOGENESIS

The etiopathogenesis of PLCA has not been clearly elucidated yet. Many studies have attempted to define the chemical nature of the dermal amyloid deposits.

The amyloid fibrils in nodular PLCA are composed of immunoglobulin light chains, termed “protein AL.” Protein AL is not unique to nodular amyloidosis and is the prevailing amyloid component in several other amyloidoses, including primary systemic and myeloma-associated systemic amyloidosis. Immunohistochemical studies have shown that the light chains in nodular amyloidosis may be of the kappa and/or lambda type. Local monoclonal plasma cells produce and secrete the light chains through an unknown mechanism, as demonstrated by light chain restriction and molecular genetics. It is thus considered a form of extramedullary plasmacytoma.¹⁻⁵ New insights have revealed that the pathology is due more to the presence of small, misfolded protein species called oligomers than to the deposition of fibrillary material. These species have been associated with cellular death and toxicity. Nonfibrillar oligomeric structures are thought to contribute to the pathogenesis of amyloid diseases supporting the hypothesis of common pathogenetic pathways.⁶

Amyloid keratin protein is found in macular amyloidosis (MA) and lichen amyloidosis (LA). The exact etiopathogenesis of amyloid deposition in these amyloidosis subtypes remains unknown. Two theories, not mutually exclusive, the fibrillar body theory and the secretory theory, have been proposed.^{7,8} The fibrillar body theory states that damaged keratinocytes undergo filamentous degeneration by apoptosis and transformation by dermal fibroblasts and histiocytes, and are converted into amyloid, which deposits in the papillary dermis. The secretion theory describes the deposition of amyloid from the degenerated basal keratinocytes at the dermoepidermal junction,

which eventually drops into the papillary dermis through the damaged lamina densa of the basal layer.⁹ Chang et al. suggested that keratinocyte destruction in cutaneous amyloidosis may occur as an initial result of apoptosis, as apoptotic keratinocytes were seen in the spinous layer and the dermoepidermal junction just above the amyloid deposits.¹⁰ The exact stimuli leading to keratinocyte apoptosis remain unknown. Factors like long-standing mechanical trauma, infectious agents, and ultraviolet radiation have been evoked. Mechanical trauma, in particular, has been reported to cause an entity called friction amyloidosis.¹¹

LA is more common in the Chinese, whereas MA is more common among Central and South Americans, Middle Easterners, and non-Chinese Asians.¹² This apparent racial incidence suggests the importance of genetic factors. The occurrence of familial cases reinforces this view. An autosomal dominant condition may be present in 10% of cases. Pathogenic heterozygous mutations have been identified in the OSMR gene in pedigrees with familial PLCA.¹³

The majority of PLCA cases are idiopathic; there is, however, an increasing number of reports that link PLCA to various immune disorders. Associations described so far include systemic sclerosis, CREST syndrome, rheumatoid arthritis, systemic lupus erythematosus, primary biliary cirrhosis, autoimmune cholangitis, Kimura's disease, ankylosing spondylitis, and autoimmune thyroiditis, the last two occurring in the same patient.¹⁴⁻²¹ A personal history of atopy may be present in patients with PLCA. However, the relationship between history of atopy and PLCA has not been either confirmed or explained.⁹

CLINICAL MANIFESTATIONS

Several clinical subtypes of PLCA have been described (Table 8.1). The most common include the macular and papular forms (MA and LA). As these subtypes may appear in the same individual concurrently, they are termed “biphasic amyloidosis” and are regarded as different manifestations of the same pathological process.¹⁻⁴

LA represents the best known form of PLCA. It typically presents as multiple, pruritic, firm, hyperkeratotic, often hyperpigmented papules that may coalesce to form thickened plaques distributed mostly on the shins. Involvement of the calves, ankles, dorsa of the feet, thighs, and extensor aspect of the arms and abdomen is not uncommon. The condition may persist for many years, with pruritus being the most prominent symptom. Differential diagnoses include mainly lichen simplex chronicus and hypertrophic lichen planus.^{1-4,9,12}



Figure 8.1 MA of the upper back.



Figure 8.2 MA of the chest.



Figure 8.3 Lichenoid amyloidosis of the chest.

Table 8.1 Suggested clinical classification of PLCA.

Papular or lichen amyloidosis
Macular amyloidosis
Maculopapular amyloidosis
Nodular or tumefactive amyloidosis
Amyloidosis cutis dyschromica

Source: Lachmann, HJ, and Hawkins, PN, in *Fitzpatrick's Dermatology in General Medicine*, ed. K. Wolff et al., 7th ed., McGraw-Hill, New York, 2008, p. 1256–65.

MA is the most subtle form of PLCA and tends to persist unchanged for years. It is clinically characterized by small brownish macules distributed in a rippled pattern, producing poorly circumscribed macular hyperpigmented areas. Lesions are more commonly distributed extensively over the upper back or confined to the interscapular area. Involvement of the back has been reported to follow chronic friction. Extremities are also common sites of involvement (shins and forearms), while the chest and buttocks are involved less commonly. The condition is associated with mild to moderate pruritus; however, itching has been reported to be absent in 20% of patients. MA may be misdiagnosed as postinflammatory pigmentation.^{1–4,9,12}

Nodular or tumefactive amyloidosis is a rare variant of PLCA. It commonly occurs on the legs, feet, trunk, face, and genitalia. It typically presents with single or more often multiple waxy, yellow-red nodules or plaques, varying in size from a few millimeters to several centimeters. Lesions are identical to cutaneous lesions of primary systemic amyloidosis. The condition follows a benign course over many years; there are, however, reports of progression to systemic amyloidosis.^{22,23}

Unusual presentations of PLCA have frequently been reported in the literature. They include macular forms of widespread diffuse pigmentation, poikiloderma-like, incontinentia pigmenti-like, and linear MA.⁹ Amyloidosis cutis dyschromica is a rare congenital form characterized by reticulate hyperpigmentation and hypopigmented macules in sun-exposed skin.²⁴

Primary cutaneous amyloidosis of the auricular concha with papules grouped on the concha of the ear is also considered a form of PLCA.²⁵

HISTOPATHOLOGY

Macular and lichen amyloidosis

Small globular deposits of amyloid are confined to the papillary dermis. Most of the amyloid is situated in the dermal papillae. Amyloid deposits do not involve blood vessels or adnexal structures. A thin band of compressed collagen may separate deposits from the overlying epidermis; sometimes the deposits are in contact with the basal cells, or at other times they are interspersed between them. Deposits may sometimes be more extensive. Pigmented cells are often seen in the dermal deposits, giving an important clue to the diagnosis of PLCA on hematoxylin and eosin

(H&E)–stained sections. Although the deposits are usually smaller in MA than in LA, differentiation of the two on the basis of the amount of amyloid is not possible. The two conditions differ in the appearance of the epidermis, which is hyperplastic and hyperkeratotic in LA.

Nodular amyloidosis

Large masses of amyloid are found in the dermis and subcutis with prominent deposition around adnexal structures and blood vessels. There is usually a marked infiltrate of plasma cells, some of them with large Russell bodies. Foreign body giant cells and focal classification may be seen. Deposits do not stain with antikeratin antibodies.

USE OF SPECIAL STAINS

Amyloid stains pink with H&E and metachromatically with crystal violet and methyl violet. It stains selectively with Congo red. Amyloid stained by Congo red gives an apple-green birefringence when viewed in polarized light. Amyloid gives a bright yellow-green fluorescence with thioflavine T. Some studies report that crystal violet is more reliable than Congo red in sun-damaged skin, which sometimes gives false-positive staining with Congo red. The cotton dye Pagoda red no. 9, used as a variant of the Congo red method, is said to be more specific for amyloid than Congo red. The amyloid in LA and MA stains with the monoclonal antibody EKH4, which recognizes 50 kDa neutral and acidic keratin. It also stains with the keratin antibody AE1. The antikeratin antibody EAB-903, which recognizes 57 and 66 kDa keratin peptides, reacts with the amyloid deposits in both LA and MA, but not with the amyloid in systemic amyloidosis. Immunoglobulins, particularly IgM, and C3 complement are found in cutaneous amyloid deposits. Most of the studies have been confined to the localized cutaneous forms. Amyloid is thought to act like a filamentous sponge with nonspecific trapping of the immunoglobulins and complement.^{26–29}

TREATMENT

Even though several treatment alternatives have been tried, the results have been unsatisfactory. Since the disease runs a chronic course and often poses an aesthetic problem, therapeutic management remains challenging.

Response to topical steroids is poor, and only mild cases might benefit from their use. Calcipotriol is of limited use as well.³⁰ There are trials that report response to topical 10% DMSO,³¹ while others report lack of efficacy.³² Treatment with ultraviolet B (UVB) has been used with some success in both MA and LA.³³ Recently, a combination of narrowband UVB and 0.1% tacrolimus ointment led to significant improvement in one case of biphasic amyloidosis.³⁴ Treatment with acitretin has been beneficial in case reports.³⁵ Therapeutic modalities like cyclophosphamide or cyclosporine seem to have only limited efficacy.^{36,37} In a case series, thalidomide at an initial dose of 100 mg daily improved clinical symptoms of PLCA.³⁸ Fractional CO₂, as well as fractional ablative erbium:YAG

laser, has recently shown good results in the treatment of MA and LA with reduction of pigmentation, thickness, itching, and amyloid deposits.^{39,40}

Low-dose amitriptyline may offer an effective and safe alternative for the treatment of pruritus.⁴¹

As interleukin 31 (IL-31) has been implicated in the pathophysiology of PCLA and other itchy dermatoses, therapies targeting IL-31 receptor might play a role in the management of the disease.⁴²

Lesions of nodular PLCA may be excised surgically or treated with curettage and cautery, cryotherapy, CO₂, or pulse dye laser. Recurrence is, however, likely.^{22,23,43}

A systematic review of PCLA performed by Kaltoft et al.¹² documented a risk of 9% for local recurrence after treatment. No correlation between type of treatment and risk of recurrence was observed. Risk of recurrence should be taken into account before planning any treatment.

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TERMINOLOGY AND CLASSIFICATION OF MASTOCYTOSIS

Mastocytosis is a rare clonal disorder characterized by excessive accumulation of pathological mast cells (MCs) in one or multiple distinct organs and tissues, such as the skin, gastrointestinal tract, and/or bone marrow (BM).¹ Mastocytosis is further subdivided into two groups that represent well-defined clinical entities: cutaneous mastocytosis (CM), which refers to forms of mastocytosis that are limited to the skin, and systemic mastocytosis (SM), which describes forms of the disease with MC infiltration of extracutaneous organs with or without skin involvement.²

Mastocytosis is a rare disorder. A prevalence of 1 per 10,000 inhabitants has been reported, but underdiagnosis is assumed.³ Both sexes are equally affected; a slight predominance of males in childhood is balanced by a female predominance in adulthood. The epidemiology of the two groups of the disease differs significantly according to age: CM is the predominant pattern in children, while 80% of cases appear during the first year of life, and in the vast majority, full remission is achieved until adolescence.⁴ On the contrary, CM represents less than 10% of adult cases, and most patients suffer from SM forms that tend to persist for a lifetime.

According to the World Health Organization (WHO),⁵ diagnosis of SM is based on one major plus one minor criterion or, in the absence of the major criterion, simultaneous detection of at least three out of the four minor criteria that are presented in Table 9.1. Besides, other clinical and biological findings and imaging data provide further information for subclassification of mastocytosis. Overall, seven categories of mastocytosis are defined by the WHO classification: (1) CM, (2) extracutaneous mastocytoma, (3) indolent SM (ISM), (4) aggressive SM (ASM), (5) SM associated with another clonal hematological non-MC lineage disease (SM-AHNMD), (6) MC leukemia (MCL), and (7) MC sarcoma.^{1,5} In addition, the WHO also defines another provisional diagnostic subtype of ISM, i.e., smoldering SM (SSM), and two new subvariants of SM and ISM have been more recently recognized, i.e., well-differentiated SM (WDSM)⁶ and ISM in the absence of skin lesions (ISM_s), respectively.⁷

The classification of CM has been based on macroscopic features of skin lesions, their distribution, or disease onset. In addition, different types of CM have been proposed based on their associations with disease progression or symptoms.⁸ A generally accepted approach is to divide CM into (1) maculopapular cutaneous mastocytosis (MPCM), also known as urticaria pigmentosa; (2) diffuse cutaneous

mastocytosis (DCM); and (3) mastocytoma of the skin. There are several subtypes of MPCM: (1) monomorphic, which is typically seen in adult patients; (2) polymorphic, which is typically seen in infants and young children; (3) plaque form; and (4) nodular form. The WHO confirmed this concept in 2001 and 2008.^{5,9} Interestingly, telangiectasia macularis eruptiva perstans (TMEP), which was considered a type of CM previously, is not included in the WHO classification. According to a recent consensus, criteria for cutaneous involvement in patients with mastocytosis include the presence of (1) a typical skin lesion (major criterion), (2) a histologically confirmed infiltrate of MCs in the dermis (minor criterion), and (3) an activating KIT mutation at codon 816 in lesional skin (minor criterion).¹⁰

According to the topic of the book, this chapter focuses on CM, as SM includes a wide spectrum of disorders with major differences in clinical course, treatment, and prognosis.

PATHOGENESIS

The pathogenesis of all forms of mastocytosis results from both chronic and episodic MC mediator release and excessive MC accumulation in one or more tissues. MCs contain a variety of vasoactive mediators and normally function to protect the body from microbial invaders and other insults by releasing these chemicals to generate inflammatory responses. The most abundant MC mediators and their biological effects are presented in Table 9.2.

The clinical manifestations associated with MC mediator release are identical to those of an allergic reaction and anaphylaxis. Apart from mediator release, some advanced forms of mastocytosis involve signs and symptoms arising from tissue infiltration by MCs, effects of local accumulations of these cells, and the presence of an associated non-MC clonal hematologic disease.

Molecular mechanisms

Somatic activating mutations of the proto-oncogene KIT are the most common casual genetic abnormalities in mastocytosis. KIT oncogene encodes a transmembrane protein KIT (CD117), which is a type III receptor tyrosine kinase. KIT is expressed by MCs, hematopoietic progenitor cells, germ cells, melanocytes, and interstitial cells of Cajal in the gastrointestinal tract. The interaction between KIT and its ligand, stem cell factor (SCF), plays a central role in regulating proliferation, growth, differentiation, adhesion, chemotaxis, and survival of MCs.¹¹ A KIT D816V mutation has been found in approximately 90% of patients with SM, irrespective of WHO SM subtype. A D816V KIT mutation in exon 17 induces ligand-independent

Table 9.1 Diagnostic criteria of systemic mastocytosis.

Diagnosis requires 1 major + 1 minor or 3 minor criteria
Major
• Presence of multifocal dense aggregates of ≥ 15 MC in BM and/or other extracutaneous tissues
Minor
• Presence of morphologically atypical MC in smears or biopsy sections of BM or other extracutaneous organs • Aberrant expression of CD25 and/or CD2 by BM MC • Presence of the KIT D816V mutation in BM, blood, or other extracutaneous organs • Serum tryptase levels of >20 ng/mL in the absence of other disorders associated with increased serum tryptase

Source: Horny, HP et al., in *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, International Agency for Research on Cancer, Lyon, 2008, pp. 54–63.

Table 9.2 Mast cell mediators in mastocytosis.

Histamine
Pruritus, urticaria, bronchoconstriction, gastric hypersecretion
Increased vasopermeability, and systemic hypotension
Proteases (tryptases and chymase)
Fibrinogen degradation, stimulation of fibroblast proliferation, activation of procollagenase, and tissue remodeling (degrade fibronectin)
Cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄)
Increased vascular permeability, vasodilation, and bronchoconstriction
Prostaglandins (PGD₂)
Vasodilation, flushing, and bronchoconstriction
Platelet-activating factor (PAF)
Increased vascular permeability, and vasodilation
Heparin
Local anticoagulant activity, osteopenia, and osteoporosis
Cytokines and growth factors (TNF-α, TGF-β, nerve growth factor, IL-3, IL-5, and IL-6)
MC and eosinophil proliferation
B-cell proliferation with polyclonal increase in immunoglobulins and paraproteins
Activation of vascular endothelial cells, cachexia, and fibrosis

Note: IL, interleukin; TGF- β , transforming growth factor-beta; TNF- α , tumor necrosis factor-alpha.

constitutive autophosphorylation of the KIT receptor, which results in dysregulation of the normal development and proliferation of MCs and, in consequence, accumulation of these neoplastic cells in tissues. Apart from the D816V KIT mutation, other less common KIT mutations have been detected in adult SM, including V560G, D815K, D816Y, D816F, and D816H.¹² However, no consistent correlation between the type of mutation and either phenotype or prognosis has been recognized.

Increased expression of SCF, the ligand for KIT, has been linked to mastocytosis lesions in the skin in a group

of adults and children with cutaneous forms of mastocytosis. Local MC hyperplasia was linked to increased free SCF in the dermis and the extracellular spaces between keratinocytes in skin samples, suggesting the increased presence of soluble SCF, although SCF in the peripheral blood was not elevated and the messenger RNA sequence was not mutated.¹³

Heritability

In the great majority of patients, mastocytosis does not appear to be inherited, although it may be present at birth. It is also not passed down to offspring, except in rare familial cases. *KIT* mutations are somatic mutations in most cases and are scarcely found in germline cells. Rare familial cases have been reported, with *KIT* mutations demonstrated in some.¹⁴

CLINICAL MANIFESTATIONS

Signs and symptoms of mastocytosis may be grouped in three categories: (1) skin findings (which may be present in both cutaneous and systemic forms of the disease), (2) symptoms arising from mediator release (which also may be present in both cutaneous and systemic forms), and (3) symptoms arising from extracutaneous organ infiltration (present exclusively in SM).

Skin signs and symptoms

In all forms of CM, as mentioned previously, the most common complaint is pruritus, which may be extremely intense, especially after exposure to a trigger, such as physical irritation or heat. Flushing and blister formation of lesions that are exposed to mechanical pressure or friction are also common symptoms in cutaneous involvement. In contrary, generalized urticarial and/or angioedema are not typical, and recurrent prominent urticaria should prompt consideration of other allergic disorders.

The most important clinical sign during physical examination in CM is Darier's sign. It is defined as the development of localized urticaria and erythema within about 5 minutes of rubbing, scratching, or stroking skin or skin lesions that are heavily infiltrated with MCs.¹⁵ This finding arises when physical irritation triggers the localized release of MC mediators. Darier's sign is present in various forms of cutaneous disease, including MPCM, DCM, and mastocytomas. Physicians must be aware that mastocytomas should not be purposefully rubbed, as this can precipitate severe symptoms of anaphylaxis and/or subsequent blistering of the lesion.

Maculopapular cutaneous mastocytosis

Lesions of MPCM are characterized by small yellow-tan to reddish-brown macules or slightly raised papules. Skin lesions in patients with childhood-onset mastocytosis are more heterogeneous than those in adults. The majority of lesions are clearly larger than those found in patients with adulthood-onset mastocytosis.¹⁶ Some of the lesions are plaques or nodules but not papules or macules. Most patients with adulthood-onset disease and cutaneous involvement

present with the characteristic small, round, brown or red monomorphic lesions (Figure 9.1). However, it should be noted that although children usually show largely homogeneous lesions of a certain type at a given time, the type can vary during the course of the disease. For example, nodules present during infancy may transform into plaques at the age of around 5–10 years and into macules after the age of 10 years before regression around puberty in the majority of patients. In a few patients, atrophic lesions with wrinkles similar to anetoderma remain after partial regression of nodules.

The upper and lower extremities are most commonly affected, followed by the thorax and abdomen. In adults, sun-exposed areas, such as the palms, soles, face and scalp, generally remain free of lesions. In children, the face and scalp may be involved. Lesions on the head often exhibit a particularly prominent Darier's sign. Pruritus associated with MPCM may be exacerbated by changes in temperature; exercise; hot showers; local friction; ingestion of hot beverages, spicy food, or ethanol; emotional stress; or certain drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs).

MPCM, except a distinct form of CM, may represent a specific form of skin involvement in patients suffering from SM. In those with systemic disease, MPCM is more typical of the less aggressive forms. Specifically, it is found in more than 90% of patients with ISM, but in less than 50% of those with SM-AHNMD or ASM.¹⁵

Diffuse cutaneous mastocytosis

DCM is the clinical entity that results from a DMC infiltration in the dermis. The skin can be either normal in color or yellowish-brown; atypical lesions, such as generalized erythema and thickened skin, may be present.

Involvement of the whole skin, rather than discrete areas, is characteristic.

This subform of CM is usually detected in early childhood and might be associated with KIT mutations other than KIT D816V, more often in exon 8 or 9. DCM can also be associated with familial mastocytosis caused by germline mutations in KIT.¹⁷

Bullous eruptions with hemorrhage can occur in patients with DCM and MPCM. Eruptions can be spontaneous or triggered by infections or, rarely, vaccinations. Blisters can be present at birth, and CM should be considered in the differential of neonatal blistering disorders.

Skin mastocytomas

Usually, mastocytoma presents as a single elevated brown or yellow lesion. Lesions are similar in quality to those of MPCM, but can extend up to several centimeters (Figure 9.2). At initial diagnosis, blistering over the lesion can be observed. A few of these children might also present with more than one lesion (multiple vs. solitary mastocytoma). Bullae may be present, with typical localization in the extremities. Upon stroking the lesion, flushing with sudden reddening of the skin and sweating may occur, while severe symptoms, including hypotension, can also occur.

Serum tryptase levels are generally normal, and no systemic involvement is found. Mastocytomas usually do not persist into adulthood. In contrast to MPCM and DCM, mastocytomas are almost never observed in adults.

Symptoms rising from mediator release

The group of symptoms associated with mediator release from MCs can occur in both CM and SM and can be either episodic, manifesting as allergic reactions and anaphylaxis,



Figure 9.1 Characteristic lesions in MPCM.



Figure 9.2 Multiple mastocytomas.

or chronic, such as complaints from the gastrointestinal system or neurological symptoms.

Allergic reactions and anaphylaxis

Acute episodes of mediator release can appear as vasodilation, hypotension, flushing, pruritus, syncope, abdominal pain, nausea, vomiting, diarrhea, fatigue, and headache. Anaphylaxis represents the most severe manifestation, with combined symptoms that typically include flushing, syncope, gastrointestinal symptoms, and vascular collapse. Urticaria and angioedema occur less frequently.¹⁸ These reactions may result from either immunoglobulin E (IgE)–mediated allergy or nonspecific activation of MCs.

Over time, chronic mediator release is associated with cachexia, chronic gastrointestinal symptoms, diffuse musculoskeletal pains, and/or tissue remodeling and fibrosis of some organs in cases of SM. Some patients have prominent anxiety and depression, which may also be due to chronic release of MC mediators; prostaglandin D₂ (PGD₂) in particular and histamine have been implicated, although the underlying mechanism remains unknown.

Gastrointestinal symptoms

Gastrointestinal symptoms can be precipitated by the same triggers that cause systemic symptoms. The most important triggers are presented in Table 9.3. Abdominal pain, diarrhea, nausea, vomiting, peptic ulcer disease, and gastrointestinal bleeding represent common signs and symptoms in both CM and SM patients. Some patients have infiltration of the gastrointestinal tract with typical-appearing MC aggregates of more than 15.¹⁹ In cases of extensive mucosal and submucosal infiltration with MCs, malabsorption may occur.

Table 9.3 Common triggers that cause mast cell mediator release in mastocytosis.

Insect stings, other venoms

- Hymenoptera
- Jellyfish
- Snakes

Drugs

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Narcotic analgesics (e.g., morphine and codeine)
- Muscle relaxants (e.g., succinylcholine, atracurium, and rocuronium during general anesthesia)
- Iodinated radiocontrast media
- Antibiotics (e.g., vancomycin)

Changes in temperature

- Cold exposure
- Heat

Mechanical irritation

- Friction
- Massage
- Pressure

Surgery and other invasive procedures (e.g., endoscopy and biopsy)

Neuropsychiatric symptoms

These manifestations are frequently observed among patients with mastocytosis but are often ignored or undertreated before the diagnosis is established. They include mood changes, lack of concentration, short memory span, increased somnolence, irritability, and emotional instability and depression. The precise cause of many of these manifestations is not known, although PGD₂ is thought to increase somnolence.²⁰

Musculoskeletal symptoms

Diffuse musculoskeletal pain of the long bones and atypical pain resembling fibromyalgia may be reported in patients with SM. Patients with SM appear to be at increased risk of developing osteopenia and osteoporosis.²¹ Therefore, a bone densitometry measurement is recommended to evaluate for osteoporosis in all patients with SM.

THERAPEUTICAL INTERVENTIONS IN CUTANEOUS MASTOCYTOSIS

In general, there are no treatment options that can change the natural course of these disorders, although prognosis in children is good. A combined strategy is needed for patients and caregivers in order to prevent the occurrence of episodic symptoms and minimize chronic complaints from the disease.

General measures

Practical interventions, such as the use of lukewarm water for bathing, air conditioning during hot weather, and avoidance of triggers for MC degranulation, are precautionary measures that help to avoid allergic reactions and anaphylaxis. Patients should avoid exposures that trigger or aggravate their symptoms to the extent possible. These exposures may include heat, humidity, cold, emotional stress, exercise, alcohol, and lack of sleep. In infants and young children, irritability, fever, teething, and skin rubbing can induce symptoms. Spicy foods, such as those containing capsaicin, may cause flushing, nasal congestion, and gastrointestinal symptoms in some patients. Patients should avoid only those triggers that bother them.

Various medications that may cause MC activation in patients with either CM or SM should be avoided when possible, unless the patient's tolerance for a specific agent is already known. Patients can be premedicated in advance of an anticipated exposure to a possible or known trigger.

Children with extensive skin involvement or elevated serum baseline tryptase may be at increased risk for anaphylaxis from a variety of triggers.²² It has been shown that among children with CM, tryptase levels of >6 ng/mL are more likely to require daily treatment to manage symptoms and prevent severe episodes, while the subgroup with levels of >15.5 ng/mL were at risk for hospitalization due to severe symptoms.²³

Epinephrine is the primary treatment for anaphylaxis. Mastocytosis patients or their caretakers should have at least two doses of epinephrine in a self-injectable form available at all times for treatment of possible anaphylaxis, since a single dose may be inadequate to counteract a massive release of mediators. Besides, patients and caregivers must be aware of the importance of lying down with the legs elevated during anaphylaxis involving hypotension. Hypotension during anaphylaxis is more common than asthma or laryngeal edema in patients with mastocytosis, and ensuring that patients are placed

in this position as soon as possible is an important therapeutic intervention.

Pharmacological treatment

The pharmacologic treatment of CM is comprised of medications to prevent MC mediator release and, when mediator release does occur, to reduce symptoms' severity.

Both H1 and H2 antihistamines are useful in the treatment of MPCM and DCM. H1 antihistamines are administered to prevent flushing and itching, while H2 antihistamines are helpful in controlling abdominal pain, heartburn, cramping, and/or diarrhea, and may enhance the antipruritic effects of H1 antihistamines.

Anecdotal evidence suggests that topical cromoglycate ointments may be symptomatically effective for the diffuse skin disease seen in some children with mastocytosis, as well as in adults with MPCM, although controlled studies are missing.²² Cromoglycate ointments at strengths ranging from 0.21% to 4% have been used in children with mastocytosis. However, these agents do not cause permanent regression of the skin lesions or influence the natural history of the disease.

Cromolyn can also be administered orally to treat gastrointestinal symptoms caused by MC mediator release, which are present in 20%–30% of patients with cutaneous disease. Some patients do not tolerate this medication due to gastrointestinal adverse effects, especially bloating and diarrhea.

Antileukotriene agents (e.g., leukotriene receptor antagonists as montelukast and 5-lipoxygenase inhibitors as zileuton) may be added for control of symptoms, such as flushing, itching, abdominal cramping, and recurrent anaphylaxis, that are suboptimally controlled by H1 and H2 antihistamines and cromoglycates. Accordingly, aspirin may be administered in adults only to control flushing, provided the patient is known to tolerate NSAIDs.

Psoralen-ultraviolet A (PUVA) therapy or narrow-band ultraviolet B (UVB) has been shown to be effective in decreasing the number of MCs and controlling pruritus that responds poorly to antihistamines.^{24,25} However, long-term use is associated with an increased risk of skin cancer, and the skin lesions usually recur after therapy is stopped. Phototherapy may be considered for temporary symptomatic relief in patients with DCM with extensive skin involvement refractory to medical management.

Short-term use of topical corticosteroids may be useful for temporarily decreasing the number of skin MCs and reducing refractory symptoms of mediator release. Localized application of topical corticosteroids may be beneficial in patients with cutaneous mastocytomas who experience local or generalized symptoms. A initial medium- to high-potency preparation, applied under an occlusive dressing for 7–10 days, is the optimal intervention. However, the benefit is short-lived, and this should not be considered a form of long-term management, especially in cases of multiple lesions or MPCM that are applied in large areas because of the side effects associated with chronic glucocorticoid use, including adrenal suppression.

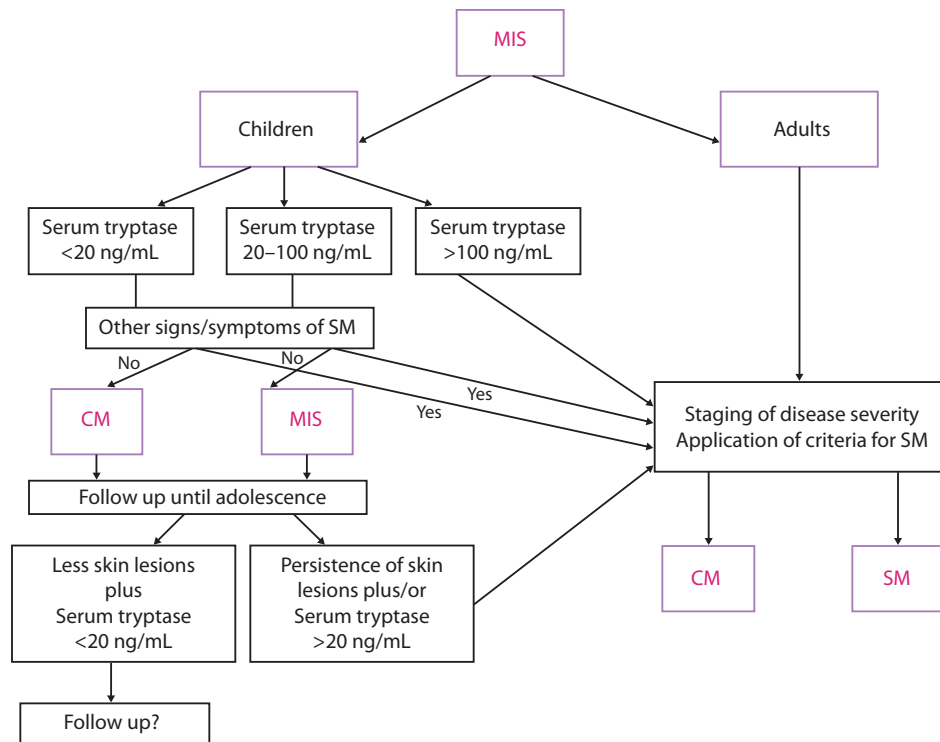


Figure 9.3 Algorithm for follow-up of patients with MIS. (Adapted from data in Valent, P et al., *Allergy*, 10, 1267–74, 2014.)

Surgical removal of mastocytomas is potentially curative if the lesion is resectable, although this is usually not necessary unless patients suffer from uncontrollable symptoms due to mediator release.

PROGNOSIS

The prognosis of cutaneous forms of mastocytosis is related to the age at presentation, while the presence of c-KIT mutations in lesional skin samples obtained from children with CM does not represent a reliable prognostic factor.

Infants and young children of <2 years

The prognosis is excellent for children with cutaneous forms of mastocytosis who have onset of skin lesions within the first 2 years of life, because in the vast majority, spontaneous resolution occurs after several years and usually before the onset of puberty.²⁶ Mastocytomas usually involute spontaneously, while lesions of MPCM in children resolve in more than 50% during adolescence, and the remaining also fade or improve progressively in most cases. A small minority may have persistent CM or may progress to systemic forms of the disease.

Risk factors for the development of systemic disease include the (1) onset of skin lesions beyond 2 years of age; (2) persistence of skin lesions beyond adolescence; (3) presence of unexplained hepatomegaly, splenomegaly, or lymphadenopathy; and (4) abnormal blood counts. In Figure 9.3, an algorithm for the evaluation of patients with mastocytosis in the skin (MIS) is presented.

Older children and adults

As already mentioned above, CM that appears after the age of 2 tends to persist. Approximately 90% of adult patients with skin lesions have evidence of systemic disease at the time of diagnosis, with the majority belonging to the category of ICM. Some rare cases of progression of pediatric-onset cutaneous disease to aggressive forms of MC disease have also been reported.²⁷

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INTRODUCTION

Pityriasis: Bran-like scales

Versicolor: Changing color

Pityriasis versicolor (synonym tinea versicolor) is a superficial fungal infection of the skin caused by the pathogenic mycelial forms of the lipophilic yeast-like fungus of the genus *Malassezia*. The most common sites are the chest and back (upper trunk)¹⁻⁴ (Figure 10.1). As its name suggests, the condition manifest in different colors (hypopigmented or hyperpigmented tan to dark brown or even black) and is generally asymptomatic (a few cases report mild pruritus), the chief concern being the cosmetic appearance of the condition.

MICROBIOLOGY (TABLE 10.1)

The causative organisms of the condition are *Malassezia* spp., which are normal human saprophytes.⁵⁻⁷ Since it is a lipophilic fungus, it is preponderant in sebaceous-rich areas like the upper trunk, which explains the most common site of involvement by pathogenic mycelial forms being the upper trunk.

With electron microscopic techniques, three distinct forms of the organism have been identified:⁸ conidia, budding yeasts, and mycelia.

The cell walls of conidia are smooth on the outer surface, while the inner surface protrudes slightly, pushing the cytoplasmic membrane into the cytoplasm.

When grown in culture, *Malassezia* may exhibit a thinner cell wall than it develops *in vivo*.^{9,10}

Mycelium is segmented and fibrils occur in the septum. Internally, the organism contains large empty-appearing vacuoles and has few mitochondria and an endoplasmic reticulum.

The most common isolated *Malassezia* species in pityriasis versicolor lesions differ among *M. furfur*, *M. globosa*, and *M. sympodialis* in reported studies.¹¹⁻¹⁴ Factors affecting this variation may be attributed to the different culture media, and perhaps ethnic, climatic, and geographic factors and characteristics of patients.¹⁵ *M. globosa* has been reported in many studies as the predominant species, with a frequency ranging between 42.8% and 97%.^{6,11,12,15}

PATHOGENESIS

Pityriasis versicolor may result from conversion of the organism (under exogenous and endogenous conditions) to the mycelial phase, which is considered the pathogenic form.

- Hypopigmented scaly lesions: The various mechanisms postulated are
 - The fungus, being lipophilic, utilizes the unsaturated fatty acids from the skin surface lipids and forms the oxidation product as dicarboxylic acids,

viz., azelaic acid, which is a competitive inhibitor of tyrosinase and decreases the melanin synthesis.

- Abnormal melanosome production is noted in the affected area.
- There is a partial block in melanosome transfer to the keratinocytes.
- The above mechanisms lead to decreased density of melanosomes within keratinocytes, with normal melanocyte density.
- The fungus acts as a sun barrier in the thickened stratum corneum.
- Hyperpigmented lesions: In hyperpigmented lesions, both increased melanin synthesis and inflammatory response with perivascular inflammation are attributed to the hyperpigmentation. The perivascular infiltrate is composed of lymphocytes, plasma cells, and histiocytes, which are involved in the immune reaction.^{16,17} *M. furfur* can also activate complement by both the classical and alternative pathways, contributing to the inflammation often seen in pityriasis versicolor patients.

Clinical features

The primary lesion is a round to oval hypomelanotic macule, usually measuring several millimeters to 3 cm, symmetrically present on the chest, shoulders, and upper back, and sometimes the lower trunk, neck, and face (Figure 10.2). Lesions are coalescent centrally and are associated with fine scaling (Figure 10.3), usually apparent by scratching or stretching the skin.

A hyperpigmented variant may be noted in some cases. Although less common, the color may vary from tan to dark brown to even black.

Diagnosis

Usually, the condition can be diagnosed clinically

Aids like Wood's light examination may help in the diagnosis of pityriasis versicolor, especially when in doubt and to rule out the differentials. Under Wood's light (ultraviolet light with a peak of 365 nm), the lesions of pityriasis versicolor fluoresce a bright yellow or gold color (Figure 10.4). This color fluorescence is characteristic of the pathogenic mycelial forms of the fungus. Also, if the fluorescence includes the areas immediately surrounding clinically visible lesions, this indicates that the infection is spreading.^{18,19} However, Wood's light provides a positive response in only one-third of cases, most likely those involving *M. furfur*.²⁰⁻²²

Confirmation of the diagnosis

Mycological examination can be used to confirm the diagnosis of pityriasis versicolor. Specimens for light



Figure 10.1 Peripherally discrete to centrally coalescent hypopigmented macules on the chest.

Table 10.1 Scientific classification of the causative fungi

Kingdom: Fungi
Phylum: Basidiomycota
Class: Ustilaginomycetes
Order: Malasseziales
Genus: <i>Malassezia</i>



Figure 10.2 Pityriasis versicolor in a less common site.

microscopic examination should be taken from the scaling edges of the lesion, as these areas are most likely to contain a larger number of microorganisms.²³ Either tape or the edge of a scalpel can be used to scrape gently a small amount of skin from the lesion, followed by



Figure 10.3 Hypopigmented macules showing fine scaling.

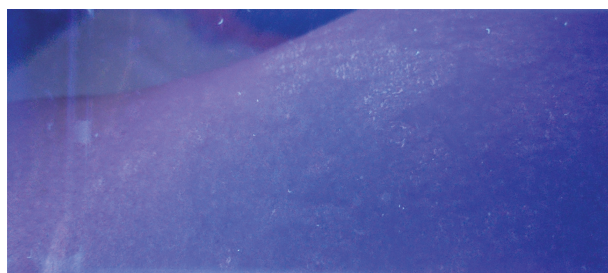


Figure 10.4 Wood's lamp examination showing yellowish fluorescence.

addition of 10%–15% potassium hydroxide to the sample, which helps dissolve the keratin and debris, and facilitates examination of fungal elements under light microscope. Light microscopic examination reveals that the yeast has a characteristic “spaghetti and meatballs” appearance, as both hyphae and spores are present.

Role of culture

Culture has no role in the diagnosis of pityriasis versicolor. As the causative agent requires a lipid-rich medium for growth, culture in standard media will not allow the yeast to grow. Also, as *Malassezia* yeasts are found in 90%–100% of the normal population,^{24,25} growth of the organism in culture does not necessarily indicate pityriasis versicolor.

A skin biopsy is usually not required for the diagnosis.

Differential diagnosis

Postinflammatory hypopigmentation (secondary to parapsoriasis), progressive macular hypomelanosis, and early vitiligo are conditions that can be differentiated from pityriasis versicolor by the absence of scaling and a wrinkled appearance of the lesions. In cases of clinical difficulty in differentiation, aids like Wood's lamp and mycological examination of the lesions easily differentiate them from pityriasis versicolor.

TREATMENT

Topical treatments

Nonspecific antifungal agents

These agents do not have activity directly against the fungus. Generally, they act by physically and/or chemically removing infected dead tissue in the stratum corneum and/or affecting cell turnover rates.²⁶

- **Selenium sulfide:** Available as a 2.5% lotion, cream, or shampoo, it has been effective in the treatment of pityriasis versicolor.^{27–29}
- **Whitfield's ointment:** Contains benzoic acid (fungistatic action) and salicylic acid (keratolytic action) in a ratio of 2:1 (usually 12%:6%).³⁰ This treatment has been shown to be effective against pityriasis versicolor.^{31,32}
- **Sulfur and salicylic acid:** Several studies have reported the effectiveness of this combination of agents in the treatment of pityriasis versicolor.^{33,34}
- **Other nonspecific agents used to treat pityriasis versicolor:** These include tretinoin cream, povidone-iodine paint,³⁵ and benzoyl peroxide.³⁶

Specific topical antifungal agents

- **Zinc pyrithione:** The efficacy of 1% zinc pyrithione shampoo versus its vehicle has been shown in two studies.^{37,38} The treatment period in both reports was 2 weeks.
- **Ciclopirox olamine:** Broad-spectrum antifungal action. The 1% cream formulation has been shown to be more effective than both the vehicle and 1% clotrimazole cream.³⁹
- **Tolciclate:** Acts by blocking sterol biosynthesis in fungal cells by inhibiting squalene epoxidase.^{40,41} Both cream and lotion formulations, each 1%, are effective against pityriasis versicolor.^{42,43}
- **Azoles:** These have a fungistatic effect, inhibiting the biosynthesis of ergosterol, and thus disrupting the formation of fungal cell membranes.
 - **Ketoconazole:** The 2% cream formulation has been reported, in a double-blind, randomized study, to be more effective than placebo.⁴⁴ Also, 2% ketoconazole shampoo and foaming gel can be effective with only 1 day of treatment.^{45,46}
 - **Clotrimazole:** A broad-spectrum imidazole reported to be effective against pityriasis versicolor in various trials.^{47–50} It is as effective as Whitfield's ointment, but more acceptable to patients.^{31,32,51}
 - **Miconazole and econazole:** These are two synthetic imidazole derivatives effective in the treatment of pityriasis versicolor. Miconazole nitrate as a 2% cream is effective when applied twice daily for 2 weeks.⁵² Econazole nitrate has been reported to be effective as a 1% foaming solution, cream, or shampoo when used once daily.^{53–55}
 - **Sertaconazole:** The 2% cream formulation applied twice daily for 4 weeks has been shown to be effective in the treatment of pityriasis versicolor.⁵⁶

- **Fluconazole:** Fluconazole is a triazole. In a 2% shampoo, it is more effective than placebo with 5 days of treatment.⁵⁷
- **Allylamines**
 - **Terbinafine:** A fungicidal agent that works by inhibiting squalene epoxidation during sterol synthesis, thus disrupting membrane synthesis in fungi.⁵⁸ Terbinafine cream, gel, and solution have been shown to be effective.^{59,60} As a 1% solution, it is more effective than vehicle with 7 days of twice daily treatment.^{61,62} It is ineffective when used as systemic treatment for this indication.⁶³

Oral treatments

Oral therapy can be more convenient and less time-consuming for the patient, and hence ensures better patient compliance. However, some prefer to reserve systemic treatment for cases in which the pityriasis versicolor involves a large area of the skin or when the disease is recurrent.

- **Ketoconazole:** This was the first effective oral azole developed against pityriasis versicolor. The drug is effective in 200 mg doses.⁶⁴ Studies have suggested that shorter courses of treatment are effective, for example, 2 weeks,⁶⁵ 10 days,⁶⁶ or even 5 days.⁶⁷ Ketoconazole is also effective in a single oral dose of 400 mg,⁶⁸ although relapse rates could be higher than with the other treatment regimens.⁶⁹ Another regimen is three 400 mg doses of ketoconazole administered 12 h apart or at 7-day intervals.⁷⁰
- **Itraconazole:** Itraconazole is effective at a dosage of 200 mg/day, when taken for either 5 or 7 days. The minimum cumulative dose for itraconazole is 1000 mg, although an improved efficacy is more likely to occur with the regimen of 200 mg/day for 7 days.⁷¹
- **Fluconazole:** There have been several open studies suggesting that fluconazole is an effective treatment option for this indication.

Oral griseofulvin and oral terbinafine are not effective against *Malassezia* infection.⁷²

Prophylactic treatment

In predisposed individuals, recurrence of the condition may be a problem despite being adequately treated for the same due to the role of endogenous factors in the conversion of this normal saprophytic fungus to the pathogenic mycelial form. Ketoconazole has been shown to prevent relapse in patients when administered at a 400 mg dose once per month or at a dose of 200 mg/day for 3 consecutive days, once per month.^{73,74} Follow-up done for up to 11 months showed a low rate of recurrence in patients receiving prophylactic treatment.

One 400 mg dose of itraconazole (four capsules of 100 mg each) given once a month for 6 months has been demonstrated to be significantly more effective than placebo.⁷⁵

Repigmentation of the hypopigmented lesions may take a few months after the successful completion of therapy, and patients need to be counseled regarding the same.

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INTRODUCTION

Idiopathic atrophoderma Pasini Pierini (IAPP) is a typically benign, asymptomatic, skin-limited atrophic condition. The precise classification and exact nosology have long been a matter of debate. It was originally considered a distinct entity, but many recent studies have suggested a link between atrophoderma and morphea.^{1,2}

In 1923, Pasini described the entity under the name “progressive idiopathic atrophoderma.”³ In 1936 in Argentina, Pierini and Vivoli studied and defined the condition and its possible link with morphea.⁴ In 1958, Canizares et al. reviewed Pierini’s findings and renamed the condition IAPP. They believed that it differed sufficiently from morphea and classified it as a distinct entity.⁵

CAUSES: PATHOGENESIS

The cause of IAPP is unknown. Some authors have suggested a role of infection with *Borrelia burgdorferi*, as it has been identified in some patients.^{1,6} There is an association between lesion development and positive anti nuclear antibodies (ANA).⁷ There are also reports of congenital IAPP.^{8,9}

PHYSICAL

The incidence of IAPP in Europe is greater than in North America. It is more frequent in whites and among women (ratio 6:1). It usually begins during the second or third decade of life. There are also cases of congenital atrophoderma.^{8,9}

IAPP manifests itself as single or multiple, well-demarcated, hyperpigmented, asymptomatic patches. There has been a single case report involving more than 200 IAPP lesions.¹⁰

The disorder begins with the appearance of a slightly erythematous lesion. Within 1–2 weeks, the lesions become hyperpigmented, violaceous, and in some cases, slate-gray to brownish with a blue hue. Over time, the pigmentation lightens. The lesions may rarely be hypopigmented¹¹ (Figures 11.1 and 11.2). Faint blood vessels may be observed in late stages.

No erythema or lilac ring is observed. The surrounding skin is normal with no palpable difference compared with the affected skin. Sometimes, white sclerodermatous indurations are seen in some parts of the lesion, reminiscent of a morphea lesion, which supports the possibility of a relation between the two disorders.

IAPP lesions spread slowly for months to years. Old lesions may slowly enlarge, but once indentation occurs, the enlargement stops. The condition follows a benign course, remaining stable for 10–20 years. The patches coalesce over time.

The affected skin appears nonindurated, soft, and thinned, remaining normal with no tenderness. The patches

are round or ovoid, varying in size from a few to several centimeters (1–12 cm). A case of a 62-year-old woman with a giant patch (27 × 23 cm) is mentioned in the literature.¹⁰

The patches have characteristic borders, their depth ranging from 1 to 8 cm. They are depressed below the level of the skin surface with well-defined borders, giving the impression of a “cliff-drop” appearance. Other descriptions commonly encountered in the medical literature are “footprints in the snow,” “Swiss cheese-like,” and “moth-eaten” appearance. This appearance is more obvious with side lighting.

The lesions may be discrete or confluent. IAPP is commonly located on the back (lumbosacral area), followed by the chest and abdomen in adolescents and young adults (Figure 11.3). A retrospective review showed that the majority of cases presented with multiple lesions, and the sites predominantly affected were the lower extremities, followed by the upper extremities and trunk, while two patients had neck and face involvement, respectively.¹¹

Most frequently, lesions are distributed symmetrically and bilaterally and oriented along the cleavage lines, while one case is reported involving a zosteriform pattern.¹² Two cases are mentioned in the literature with a unilateral distribution.^{11,13}

Histological features

An elliptical biopsy should be obtained from the edge of the lesion and deep enough to include the subcutaneous tissue, making it easier to detect the transition between normal and lesional dermis. The histological features are usually nondiagnostic. The epidermis is normal or slightly thin and atrophic, while melanin may be increased.

In mid- and reticular dermis, the collagen bundles are presented homogenized and hyalinized, in most cases indistinguishable from those of normal skin.^{1,6} Dermal thickness is reduced. The appendages are preserved, as are the sweat glands and pilosebaceous units. The elastic tissue strain is essentially normal.^{2,5,6,9} Changes of elastic fibers on Gieson and/or Giemsa stains vary within the spectrum from normal to severe diminution with fragmentation (anetoderma-like).¹¹ In order to designate the fragmentation of elastic fibers, Carrington et al. suggested the term *atrophoderma elastolytica discreta*.¹⁴ There are some reports of a decreased amount of elastic fibers in the dermis.^{2,13,15,16}

Mild perivascular or perifollicular mononuclear infiltrate may exist, but it was absent in most of the biopsy specimens in the study of Saleh et al.¹¹

Laboratory studies

Routine blood and urine studies do not help in the diagnosis of IAPP.



Figure 11.1 IAPP erythematous and violaceous lesions on the right side of a male's trunk.

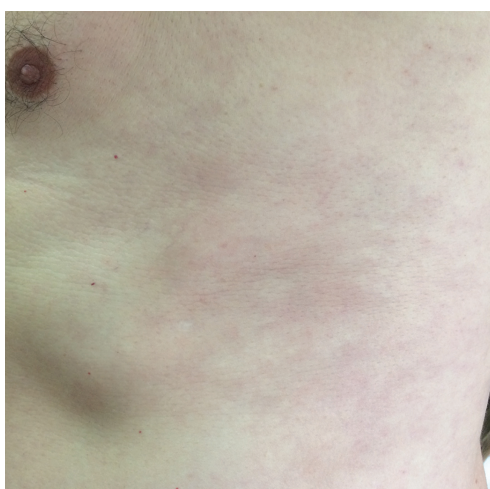


Figure 11.2 Same patient with similar lesions on the left side of the trunk.



Figure 11.3 Location of IAPP lesions on the lumbosacral area.

Screening tests such as the Western blot may be performed to determine the presence of anti-*B. burgdorferi* antibodies.

Direct immunofluorescence is usually nonspecific or negative.^{1,17} Immunoglobulin M (IgM) and C3 may be deposited at the dermoepidermal junction. Reduction of CD34 is observed.¹⁸

Ultrasound (B mode) can designate the thickness of the dermis, and subcutis¹⁹ MRI may exhibit dermal atrophy.²⁰

Differential diagnosis

Skin disorders resembling IAPP are late-stage morphea, lichen sclerosus et atrophicus, postinflammatory hyperpigmentation, atrophoderma of Moulin, systematized epidermal nevus, and anetoderma.

The hyperpigmentation of IAPP is a feature not seen in lichen sclerosus et atrophicus or panniculitis. On the other hand, the palpation of anetoderma (saclike protrusion) and histology that reveals loss of dermal elastic fibers can distinguish the two entities. It is very important to differentiate between anetoderma and atrophoderma because the former may be associated with severe disorders, such as systemic lupus erythematosus (SLE),²¹ HIV infection,²² antiphospholipid syndrome and prothrombotic abnormalities.^{23,24} The atrophoderma of Moulin follows Blaschko's lines.

Much debate has centered around the proper classification of atrophoderma. Some authors regard it as a distinct entity, while others believe that IAPP is a variant of morphea (superficial morphea).¹⁰

Morphea is a pigmented, benign, and asymptomatic disorder with violet or brownish skin lesions. It begins as an erythematous plaque with a characteristic peripheral lilac ring. The center of the plaque is often whitish and sclerotic. The histological features of morphea include dermal sclerosis; lymphoplasmacytic infiltrate, perivascular and interstitial; and eccrine gland entrapment.

The authors who support the relation between IAPP and morphea present several arguments. First, there are clinical and histological similarities between the end stages of morphea and IAPP.^{1,2,5} Moreover, morphea-like induration has been reported in IAPP lesions.^{2,5,6} Some clinicians believe that IAPP is an abortive form of morphea, in which induration failed to develop.^{1,2,17} Another argument that corroborates the relation between the two entities is the fact that morphea plaque may coexist with IAPP in the same patient.^{1,2,16,25} The opinion of Miller et al. is that IAPP and morphea can transit to each other at any time during the course of disease.²⁶

On the other hand, the supporters of the opposing opinion have their own arguments. First, they both have their own distinguishable clinical and histological features. IAPP has the characteristic "cliff-drop" border but not the "lilac ring" of morphea. IAPP's onset is early, and the progression is longer than morphea's (16–20 vs. 5 years). It begins with atrophy and may develop induration, while morphea begins with induration and progresses to atrophy.²⁶

Histologically, inflammation and loss of appendageal structures are present in morphea but not in IAPP. Another feature is the decreased number of fibers of IAPP and the normal ones in morphea.⁵ Canizares et al. suggested two varieties of IAPP. The first one is closer to scleroderma, and the other is idiopathic with its own characteristics.^{5,10} Furthermore, ANA, C3, C4, and rheumatoid factor are normal in IAPP.^{17,18}

In conclusion, in 2000 Yokoyama et al. mentioned the different glycosaminoglycans extracted from IAPP than those extracted from morphea.²⁷

Comorbidities

The co-occurrence of IAPP and morphea has been noticed in some cases. They may appear in different areas of the same individual,¹¹ or arise within the atrophic hyperpigmented plaque as reported in the case of a giant lesion of IAPP.¹⁰

Kim and Lee reported an overlap between IAPP and juvenile idiopathic arthritis.²⁸ Kopeć-Medrek et al. suggested thyroid gland evaluation in all patients with scleroderma-like disorders.²⁹

Treatment

There is no effective treatment. Topical and systemic steroids are the most common medical approach. The standard recommended therapy for Lyme disease could be an option in cases with a positive *B. burgdorferi* antibody titer.³⁰

Carter et al. reported that antimalarials such as hydroxychloroquine could be an option for chronic refractory IAPP.⁷

Psoralen-ultraviolet A (PUVA), potassium benzoic acid, D-penicillamine, and retinoids have all been used with variable efficacy. Aprey et al. reported a single case in which a 50% reduction of hyperpigmentation was observed with treatment using a Q-switched Alexandrite laser.³¹

Follow-up

Ultrasonography could be effective for follow-up. The entity is benign, runs a protracted course, and may self-resolve with no complications. Patients should protect affected areas from the sun, exposure to which can lead to a darkening of the lesions.

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INTRODUCTION

The term *poikiloderma* refers to a combination of linear telangiectasia, mottled hyperpigmentation, and superficial atrophy in a reticular pattern.¹ Poikiloderma of Civatte (PC) is a common, acquired poikiloderma of the face and neck. It is clinically important due to the significant cosmetic disfigurement it may produce.² It was originally described in 1923 by the French dermatologist Achilles Civatte as “reticular pigmented poikiloderma of the face and neck.”³ The term *Civatte’s disease* was coined by E.G. Graham-Little in 1928.⁴

EPIDEMIOLOGY

PC is common. In a Greek study among dermatologic patients, the incidence was estimated to be 1.4%.⁵ However, the true prevalence is unknown. PC most often occurs in middle-aged and elderly individuals.^{2,5} It is most often seen in women at a perimenopausal stage, including iatrogenic menopause. In a review by Pierini and Bosq, there were 44 females among 47 PC cases in total.⁶ In a recent study of 50 cases, women predominated (68%) and the majority of them were at a perimenopausal stage (76.4%).⁵ PC seems to also be common in males, but it is probably underreported because many do not seek medical advice. Interestingly, PC was diagnosed at an older age among males: mean age 61.7 years (range 48–74 years) versus 47.8 years (range 39–68 years) among females.⁵ Lighter-skin phototypes (I–III) are more commonly affected, as well as those engaged in outdoor occupation or leisure activities.² A study from Norway suggested that a relationship might exist between PC and video display terminal work.⁷ Interestingly, nonmelanoma skin cancer is associated with PC less frequently than expected.⁵

ETIOLOGY AND PATHOGENESIS

The etiopathogenesis of PC appears to be multifactorial.

Involvement of sun-exposed areas of the neck and face, while anatomically shaded areas are spared, suggests that solar radiation plays a major role.² Age distribution, especially in males,⁵ implicates a cumulative chronic pattern of sun exposure.

Familial cases of PC have been reported, and a genetic basis has been suggested.⁸ In addition, the occurrence of PC, in the absence of all suspected causal factors, provides further support to the speculation that a genetic predisposition to the disease may exist. An analysis of seven PC cases among members of two unrelated Greek families showed that the mode of inheritance is consistent with an autosomal dominant trait with variable penetrance.⁸

The age and sex distribution of the patients, as well as the well-known association with menopause, suggests that hormonal factors, namely, low estrogen levels, in combination with the chronoaging process, may be also involved.^{2,5,9,10}

It has been speculated that photoactive substances in perfumes and cosmetics possibly induce a photoallergic or phototoxic reaction that triggers the disease process.² Patch testing was performed in 32 PC patients, using the European standard series and the fragrances series.⁹ Thirteen (40.62%) had one or more positive reactions to allergens of the standard series. Nickel sulfate was the most common cause of contact sensitization (18.75%). Eight patients (25%) had positive reactions to fragrance mix and/or balsam of Peru or to allergens of the fragrance series. A statistically significant difference in the frequency of positive reactions to fragrances between the PC group and the control group (χ^2 value = 3.91, $p < 0.05$) was documented. Photopatch testing with the photoallergens series was negative in all patients.⁹ Phototesting with a monochromator showed in all cases a minimal erythematous dose within normal limits for all ultraviolet (UV) wavelengths examined.⁹ Based on positive patch testing results, a role for methylchloro-isothiazolinone/methylisothiazolinone (Kathon) in the development of PC has been proposed.¹¹ Vachiramon and Wattanakrai reported a 49-year-old woman with PC and a positive photopatch testing reaction to 6-methylcoumarin (found in the patient’s perfume), suggesting that photoallergic contact sensitization may also play an important role.¹² It appears that at least in a subset of PC patients, contact or photocontact sensitization, mostly to perfume ingredients, may play a pathogenetic role.

PC, as well as erythematotelangiectatic rosacea, affects mostly fair-skinned middle-aged women. Clinically, they present with erythema, linear telangiectasia, and episodes of flushing. Solar elastosis of the upper dermis is the predominant histological feature. On the basis of these similarities, it has been suggested that PC and rosacea may represent variants in the same nosological spectrum.¹³

Katoulis et al. have proposed a histopathogenetic scenario for PC.^{9,10,14} In genetically predisposed individuals, sun-induced damage of the dermal connective tissue (solar elastosis) results in telangiectasia due to loss of vascular support. In perimenopausal females, these changes are augmented by the decreased estrogen levels that affect the rate of collagen production. Chronoaging probably offers a favorable setting, contributing to the atrophic changes. Application of perfumes and cosmetics may induce a delayed contact or photocontact hypersensitivity reaction, causing basal cell changes and leading to melanin incontinence that presents clinically as mottled hyperpigmentation. In this way, the triad of poikiloderma is completed.¹⁴

CLINICAL PRESENTATION AND COURSE

PC typically presents with reticular patches, pink to dark red in color, symmetrically involving the V, the sides of the

neck, and the upper chest (Figures 12.1 and 12.2). Sparing of the anatomically shaded areas, that is, the submental region and the anterior aspect of the neck, is highly characteristic.^{2,5} It usually starts from the V of the neck and spreads slowly.⁵ Facial involvement, observed in 38% of the cases in one study,⁵ is usually mild and limited to the parotid region or chin. A case of PC with extracervical involvement, i.e., affecting the forearms of a woman practicing aromatherapy, has been recently reported.¹⁵

The condition is often asymptomatic. Occasionally, a mild pruritus or a burning sensation is reported.^{2,5} Patients, not uncommonly, complain of a rosacea-like flushing.⁵

Based on the predominant clinical feature, PC has been classified into erythematotelangiectatic, pigmented, and mixed types.⁵ Among them, the erythematotelangiectatic type appears to be the most common.

The condition is only of cosmetic concern. The course is chronic, slowly progressive, and irreversible. No spontaneous improvement is expected.



(a)



(b)

Figure 12.1 (a and b) Erythematotelangiectatic type of PC in a postmenopausal female.



Figure 12.2 Pigmented type of PC in an elderly male.

HISTOPATHOLOGY AND ELECTRON MICROSCOPY

The histologic picture of PC is characteristic, but not pathognomonic. The most prominent and constant feature is solar elastosis. In a histological study of 50 cases,⁹ findings included solar elastosis of the papillary dermis (100%), flattened (84%) and atrophic (62%) epidermis, basket-weave orthokeratotic hyperkeratosis (92%) with occasional follicular plugging (34%), mild or patchy vacuolar degeneration of the basal cell layer (46%), melanin granules irregularly distributed in the lower epidermis (94%) and melanophages laden with melanin in the dermis due to melanin incontinence (92%), mild perivascular lymphohistiocytic inflammatory infiltrate in the papillary dermis (78%), dilated and hyperemic blood vessels (96%), and increased numbers of mast cells in perivascular distribution (22%).

In an ultrastructural study of 10 patients,⁹ the epidermis showed only minor changes: a focal distention of the perinuclear pool in the basal cells, associated with degenerative changes of the adjacent nuclear membrane; the dermoepidermal junction was intact. In the papillary dermis, the collagen fibers were swollen and disrupted and there was focal degeneration of the collagen bundles. At these sites, inactive fibroblasts could be seen between the collagen bundles, as well as ill-defined foci of microgranular or microfibrillar texture, containing degenerated organelles, most probably mitochondria. In two cases, several vacuolar spaces of varying size and shape were found just under the basal lamina. In most cases, melanin-laden macrophages (melanophages) were detected and several electron-dense bodies (pigment granules) randomly scattered in the dermis. The endothelial cells of the dilated dermal blood vessels were normal.

DIFFERENTIAL DIAGNOSIS

PC must be differentiated from other causes of reticulate or mottled pigmentation of the neck,¹⁶ primarily Riehl's melanosis and erythromelanosis follicularis faciei et colli.

In Riehl's melanosis, spotted brown pigmentation predominates, commonly located on the face, forehead, and temples. Lesions are less reticular, while telangiectasia is minimal or absent.⁶ Discontinuation of offending cosmetics results in a dramatic improvement.^{17,18}

Erythromelanosis follicularis most commonly affects young males. It is characterized by a combination of brownish-red hyperpigmentation, telangiectasia, and follicular keratosis involving the peripheral face and/or neck.¹⁹

Differential diagnosis also includes congenital poikilodermas. These are characterized by early onset and association with other abnormalities, such as those seen in Bloom's syndrome and Rothmund-Thomson syndrome.

Differentiation of PC from poikiloderma associated with collagen vascular disease and poikiloderma vasculare atrophicans should be based on its strict anatomic localization on the sun-exposed face and neck, the absence of systemic manifestations, and a benign course. Other conditions to be considered include chronic graft versus host disease, berloque dermatitis, and friction melanosis.⁵

TREATMENT

Treatment of PC is challenging. The ideal treatment should address both pigmented and vascular components at the same time. Identification of clinical type should guide the selection of an appropriate therapy. Guidelines for treatment do not exist.

Various modalities have been tried with differing results. Electrosurgery can be used to treat telangiectasia, but it is time-consuming and may cause scarring or residual dyschromia.²⁰ Cryotherapy is ineffective. Depigmenting agents, such as 2%–4% topical hydroquinone, 15%–20% topical azelaic acid, or kojic acid, may be useful as an adjuvant therapy for the pigmented type of PC.²¹ Topical retinoids and chemical peels can improve photoaged skin.²² Topical flavonoids may reduce erythema, thus improving cosmetic appearance.⁵

Lasers are the treatment of choice for PC. The major problem with laser treatment for PC is that it is costly and not consistently effective. The pulsed dye laser (PDL) at 585 nm is safe and effective in treating vascular lesions, including PC.²¹ Several sessions are needed. Treatment with the first-generation flashlamp PDL yielded variable results in small numbers of patients.^{22,23} The vascular component of PC responded well to treatment, while the hyperpigmentation showed only minimal improvement. In a series of seven patients treated with PDL, only one patient developed scarring 4 months after treatment.²⁴ Newer PDL devices with a longer pulse duration (1.5 ms) and 10 mm spot size appear to be more effective. Adverse events include marked posttreatment purpura, a mottled appearance, hyperpigmentation, occasional hypopigmentation, and atrophic or hypertrophic scarring. Eight patients with PC were treated at 3-month intervals with PDL at a 585 nm wavelength, using a 7 or 10 mm spot size, a fixed pulse duration of 450 ms, and fluences between 3.5 and 7 J/cm².²⁵ All patients had good results with respect to clearing of the vascular component. Six of them, treated with 5–7 J/cm², reported severe depigmentation 4–11 months after treatment.²⁶

Quasi-continuous wave lasers, such as the argon-pumped tunable dye laser (APTDL), copper vapor laser, krypton laser, and potassium titanyl phosphate (KTP) laser, can also be used to treat PC. They carry a higher risk of complications, but they are not associated with postoperative purpura.²⁷ They may prove useful in treating larger-caliber vessels. A single case of PC successfully treated with the KTP laser at 532 nm has been reported.²⁸

Successful treatment of PC cases has been reported with fractional photothermolysis.²⁹ The 1550 nm wavelength emitted largely targets tissue water and not melanin, creating thousands of targeted microthermal treatment zones and sparing the surrounding tissue. In a prospective pilot study in 10 PC patients, ablative fractional photothermolysis was both safe and effective for the treatment of the vascular, pigmentary, and textural components of PC. The number of treatments required for improvement of PC ranged from one to three at 6- to 8-week intervals, with an average of 1.4. For erythema/telangiectasia, the mean score improved 65.0%; for dyschromia, 66.7%; for skin texture, 51.7%; and for skin laxity, 52.5%.³⁰

Intense pulsed light (IPL) systems are high-intensity light sources that emit noncoherent polychromatic light in a broad-wavelength spectrum of 515–1200 nm, permitting treatment of both vascular and pigmented components simultaneously.³¹ IPL sources have been used in PC with results comparable to those of PDL, as far as efficacy and safety are concerned.³² One hundred and thirty-five unselected PC patients were treated with IPL. After one to five treatment sessions, a 75% improvement of telangiectasias and hyperpigmentation was observed. Side effects, mostly pigment changes, occurred in 5% of the patients.³³ In another study, 66 patients with typical PC were treated with IPL every 4 weeks. A 50%–75% improvement in both telangiectasias and hyperpigmentation was observed after an average of 2.8 treatments. The incidence of hypopigmentation was 5%.³⁴ A total of 175 patients with PC were subjected to a treatment protocol with IPL at various settings. Clearance of more than 80% of vascular and pigmented components of PC was observed. Minimal and transient side effects occurred in 5% of the patients.³⁵ In a recent study, Campolmi et al. treated 28 PC and 35 rosacea cases with IPL for 2 years at three weekly intervals.³⁶ Of the 63 patients in total, 51 had a marked improvement, 10 had moderate improvement, and 2 had only a slight improvement. No significant undesirable effects were observed.

PREVENTION

Strict photoprotection is fundamental. Detailed instructions should include sun avoidance, remaining in the shade, wearing a hat and sun protective clothing, and proper use of a broad-spectrum sunscreen of at least sun protection factor 30. Avoidance of perfumes, especially avoiding the direct application of perfume on the skin, is recommended. In view of the possible role of contact sensitization, evaluation of patients with patch testing and avoidance of documented allergens may be helpful for an effective management of PC.

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INTRODUCTION

Benign and malignant nonmelanocytic skin lesions may present as pigmented macules or nodules that, especially on sun-damaged skin, have to be differentiated from melanoma. Here we provide an overview of the clinical and dermoscopic presentation of the most common benign pigmented nonmelanocytic lesions, including solar lentigo (SL), seborrheic keratosis (SK), actinic keratosis (AK), lichen planus–like keratosis (LPLK), and dermatofibroma (DF). A focus on pigmented nonmelanocytic malignant skin tumors is also presented, with particular attention to basal and squamous cell carcinoma (BCC and SCC).

LENTIGO

A lentigo is a sharply circumscribed, pigmented macule, histologically characterized by hyperplasia of the epidermis and increased pigmentation of the basal layer. A variable number of melanocytes are present; they may be increased in number, but they do not form nests.

Multiple clinical and etiologic varieties exist. Lentigines have a role as a marker for ultraviolet (UV) damage.^{1–3} Moreover, their role as a sign of systemic syndromes is of major significance.

Lentigines are observed worldwide.⁴ The incidence depends on the type of lesion.

Lentigo simplex

Lentigo simplex (e.g., simple lentigo and juvenile lentigo) is the most common form of lentigo, not induced by sun exposure and not associated with systemic disease.⁵ Clinically, the lesions are round or oval asymptomatic macules. Pigmentation is evenly distributed, with a color ranging from brown to black. The lesions are few in number and may occur anywhere on the skin or mucous membranes. They appear first in early childhood, but they can also be present at birth or develop later.

Solar lentigo

SL (also called actinic lentigo, senile lentigo, sun spot, and liver spot) is the most common benign sun-induced lesion that occurs in sun-exposed areas. SL most commonly appears on the face, arms, dorsum of the hands, and upper part of the trunk. The lesions are usually brown, but the color may range from yellow-tan to black. Older lesions are often dark brown or brownish black, and slowly increase in number and size over time.^{1,2}

Ink-spot lentigo

Ink-spot lentigo (i.e., reticulated black SL) can be distinguished by a wiry or beaded, markedly irregular outline;

these lesions occur in Caucasians. The benign lesions have a reticulated pattern, and most lesions resemble a spot of ink. The distribution is limited to sun-exposed areas of the body, similar to that of SL. The most common presentation includes one ink-spot lentigo among an extensive number of SLs.

Oral and labial melanotic macules

Oral and labial melanotic macules are similar to each other. Labial lesions almost always occur on the vermilion of the lower lip, and their color ranges from brown to blue to blue-black. The lesions are usually solitary, symmetric, and asymptomatic. The differential diagnosis should include Laugier–Hunziker syndrome and Peutz–Jeghers syndrome.^{6,7} The absence of systemic features and involvement at other sites allow differentiating oral and labial melanotic macules from these syndromes.

Vulvar and penile lentigo

Vulvar and penile lentigo are benign lesions similar to labial melanotic macules. In men, the most common sites are the glans penis, corona, corona sulcus, and penile shaft. In women, the lesions appear anywhere on the genital mucosa as a mottled, pigmented patch.

Syndromes characterized by the development of multiple lentigines

Xeroderma pigmentosum

Xeroderma pigmentosum (XP) is an autosomal recessive condition consisting of an inability of cells to repair DNA damage induced by exposure to UV light and certain chemicals. Clinically, patients have skin atrophy and progressive pigmentary changes, including multiple lentigines. Subsequently, neoplastic changes occur on the skin, often in childhood. SCC and BCC are the most common malignancies.⁸

LEOPARD syndrome

LEOPARD syndrome (lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and deafness syndrome) is a complex genetic disorder that is transmitted as an autosomal dominant trait with variable penetrance. A mutation of the PTPN11 gene may be documented.⁹ Lentigines are present at birth and increase in number until puberty. The intensity of the pigmentation varies. The lesions are numerous on the neck and trunk, but they can also be widespread and involve the genitalia, palms, soles, and scalp.

Peutz–Jeghers syndrome

Peutz–Jeghers syndrome is an autosomal dominant condition with a high degree of penetrance and is characterized by gastrointestinal polyps and pigmented macules. Lentigines usually arise in early childhood, and they have a characteristic distribution around the mouth, on the lips, and on the buccal mucous membranes. Additionally, lesions appear on the fingers and toes on both the palmar and volar surfaces. Lesions are characteristically absent on the flexor and extensor surfaces of the rest of the body.⁶

Laugier–Hunziker syndrome

Laugier–Hunziker syndrome is characterized by a variable number of pigmented macules that most commonly appear on the lower lip, buccal mucosa, hard palate, and occasionally, tips of the fingers. The lesions mostly occur on the nails. This syndrome differs from Peutz–Jeghers syndrome because of the absence of intestinal polyps.⁷

Myxoma syndrome

Myxoma syndrome is associated with mucocutaneous lentigines, along with various additional abnormalities. Some constellations of abnormalities have been given specific names: LAMB syndrome (lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi) and NAME syndrome (nevi, atrial myxoma, myxoid neurofibroma, and ephelides).

Carney syndrome

Carney syndrome is an autosomal dominant multiple neoplasia syndrome involving cardiac, cutaneous, and mammary myxomatous masses, lentigines, blue nevi, endocrine disorders, and testicular tumors.¹⁰

Dermoscopy features

Dermoscopy features have been described especially for SLs, because of their differential diagnosis with melanocytic lesions.^{11–14} Dermoscopy of lesions occurring on the trunk and extremities can be variably characterized by a brown homogeneous pattern, thin pigmented network, or fingerprint structures (Figure 13.1).

Peculiar dermoscopy features for SLs occurring on the face have been described. Because of the anatomy of facial skin, a pigmented pseudonetwork can be detected. In this case, the holes of the network are represented by follicular and sweat gland openings (Figure 13.2).

The border of the lesions is often characterized by the so-called “moth-eaten edge,” recognizable as a nonuniform concave area resembling a “bite” at the periphery of a lesion.

Ink-spot lentigo reveals a distinctive appearance. A asymmetric reticular pattern, with a thickened pigment network (broken-up network) showing irregular and wide meshes, is the hallmark of ink-spot lentigo. This reflects the particular epidermal architecture marked by pronounced

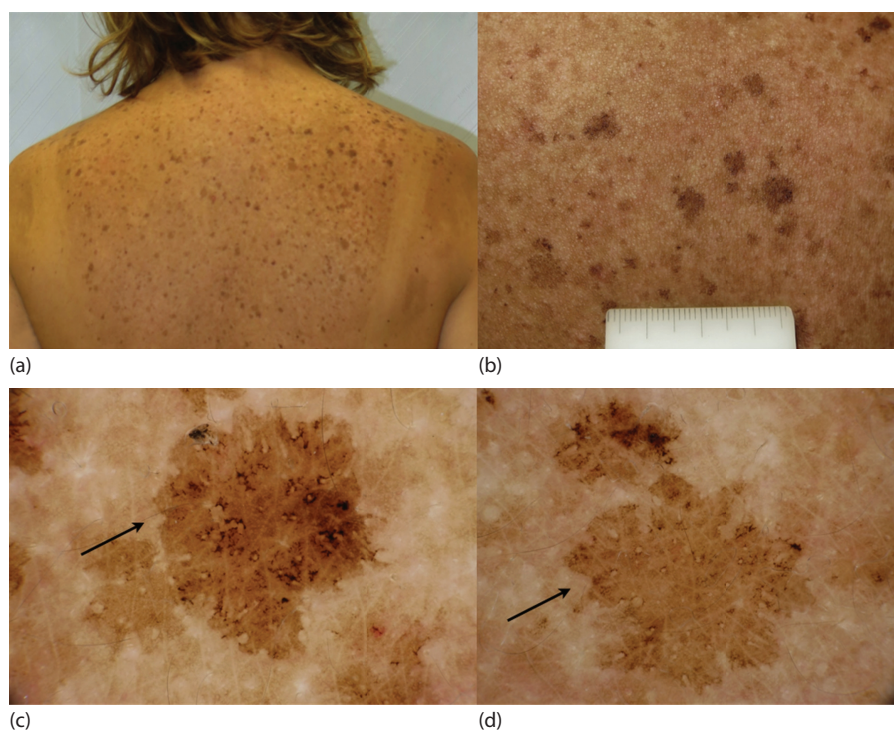


Figure 13.1 Clinical (a and b) and dermoscopy (c and d) image of multiple SLs on the back of a 45-year-old woman. (a) Clinically, multiple light to dark brown macules are detected, representing a marker of sun damage. (b) Close-up of the clinical image. (c and d) Under dermoscopy, the lesions are characterized by a thin network, varying in color from light brown to dark brown, and moth-eaten borders (arrows).

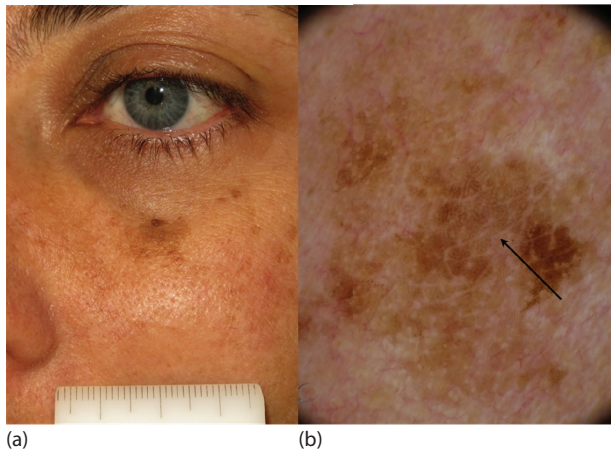


Figure 13.2 An SL on the face of a young, fair-skinned woman. (a) Clinically, a light brown macule with ill-defined borders is detected. (b) Under dermoscopy, a homogeneous light brown pigmentation is detected, with areas of fingerprinting (arrow).

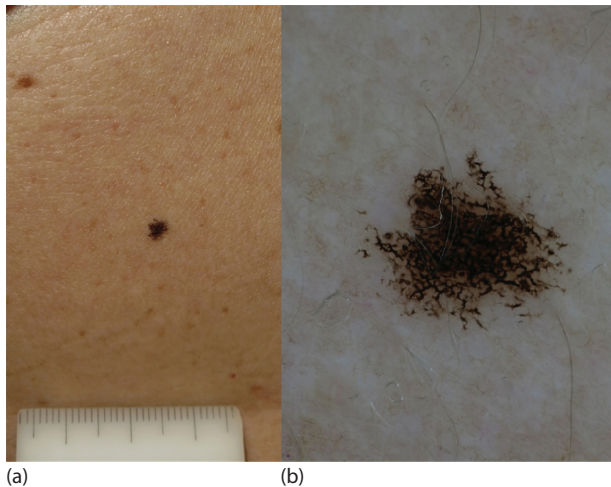


Figure 13.3 Ink-spot lentigo. (a) Clinical appearance of a small, black macule on the back of a 50-year-old man. (b) Dermoscopy, a superficial asymmetric reticular pattern is detected, with a thickened pigment network showing irregular and wide meshes.

pigmentation of the tips of elongated rete ridges and by the nearly complete absence of epidermal pigmentation covering the suprapapillary plates (Figure 13.3).

SEBORRHEIC KERATOSIS

SK is a benign, very common epithelial skin neoplasm. The frequency appears to increase with age. SKs have a variety of clinical appearances, and they develop from the proliferation of epidermal cells. SKs are less common in populations with dark skin than in those having white skin. However, black individuals develop a variant of SK termed dermatosis papulosa nigra. These lesions affect the face, especially the upper cheeks and lateral orbital areas;

they are small, pedunculated, and heavily pigmented with a minimal keratotic element.¹⁵

Clinical features

SKs appear on any body site except the palms and soles, but are most frequent on the face and trunk. They usually begin as flat, sharply demarcated, brown macules. Later on, SKs may develop an uneven, papillated surface. Their coloration varies from yellowish to opaque brownish-black. Although the clinical diagnosis of most SKs can be made easily, in some instances, due to their many clinical faces, even experienced clinicians may have diagnostic problems.

Histopathology

These lesions are raised above the skin surface, and they show a papillomatous epithelial proliferation containing horn cysts. They do not have a tendency toward malignancy. Many variants can be observed. The acanthotic pattern is the most frequent, in which a thick layer of basal cells is observed interspersed with pseudohorny cysts. Invaginations to form keratin-filled pseudocysts are present. Some of these cells contain melanin.

Hyperkeratotic SKs have pronounced hyperkeratosis and papillomatosis with less acanthosis. The reticulated or adenoid types have less epidermal thickening, and horn pseudocysts are usually less prominent. Marked hyperpigmentation is often present, and they have some histologic similarity to SL. The clonal SKs show well-demarcated nests of basaloid or larger squamous cells within an acanthotic SK. Melanoacanthoma is a deeply pigmented SK in which an acanthotic proliferation of large dendritic melanocytes is identified. Lichenoid SK is an inflammatory variant.¹⁵

Dermoscopy features

The three major types of SK, namely, acanthotic, reticulated, and verrucous, display different dermoscopic features. These features are usually distinctive, and the diagnosis of SK can be made easily; however, in some cases differential diagnosis with skin malignancy is not readily made. Uncommon variants include clonal SK (Borst-Jadassohn phenomenon), melanoacanthoma, and LPLK, which can clinically and dermoscopically simulate other skin neoplasms, BCC, and melanoma. Irritated SKs can also be of difficult differential diagnosis, because they may display an atypical vascular pattern.¹⁶⁻²⁷

Acanthotic type

The dermoscopic hallmarks of acanthotic SK are few to numerous milia-like cysts (whitish or yellowish structures that correspond to small, intraepidermal, keratin-filled cysts) and several comedo-like openings (keratin-filled invaginations of the epidermis) (Figures 13.4 and 13.5). The background coloration varies from an opaque light brown to dark brown or even black pigmentation. Lesions are usually characterized by a sharp demarcation, sometimes with the so-called moth-eaten borders, defined as concave areas at the edge of a lesion.

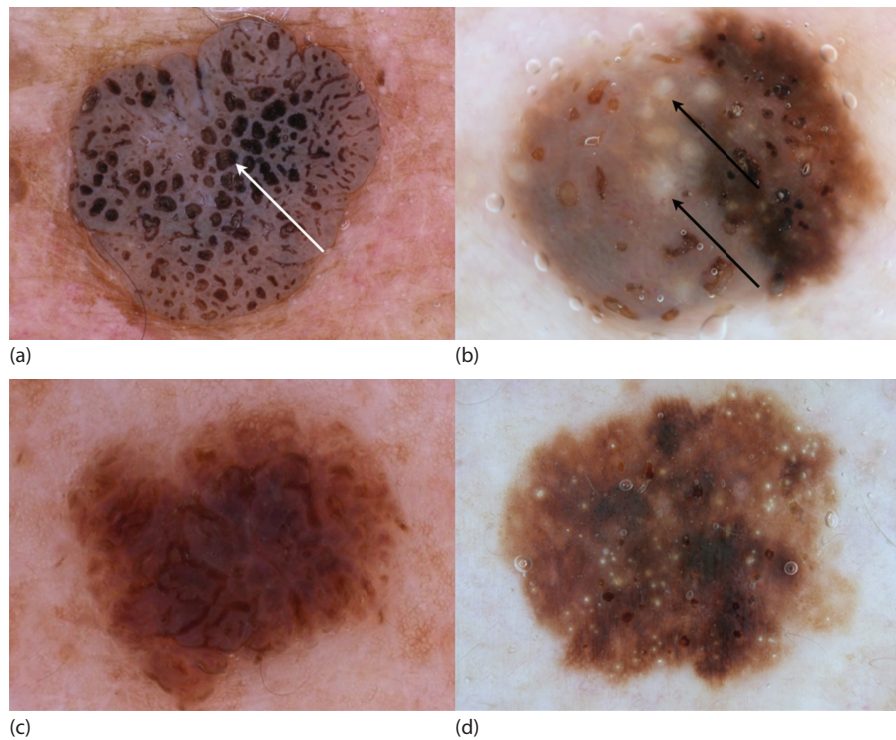


Figure 13.4 Dermoscopy of SK. (a) A dark brown homogeneous pigmentation, well-defined borders, and multiple comedo-like openings (white arrow). (b) Multiple comedo-like openings and milia-like cysts (black arrows). (c) Brain-like appearance of an SK. (d) Multiple milia-like cysts and comedo-like openings.

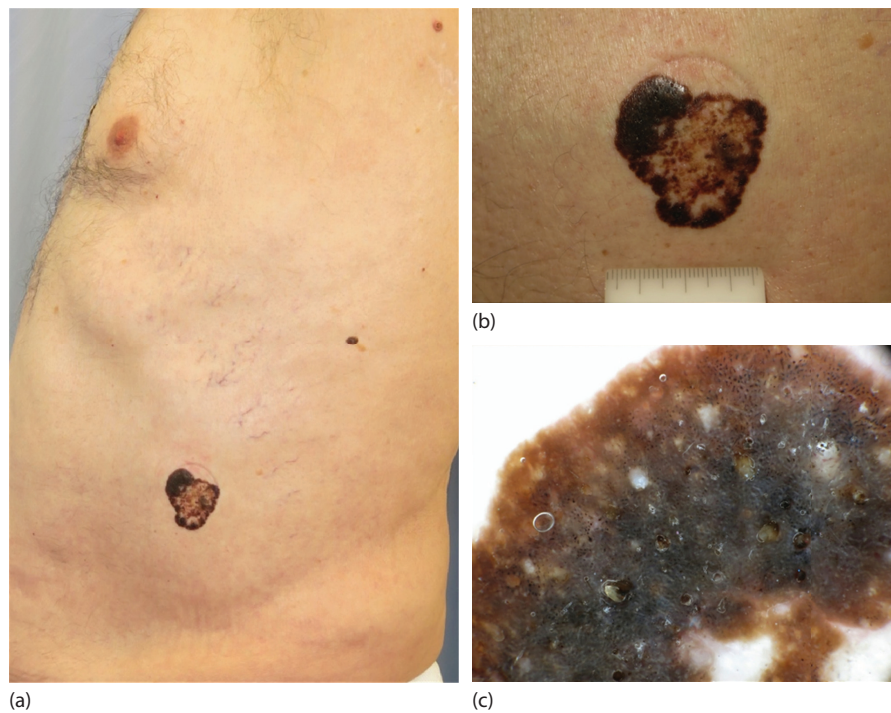


Figure 13.5 Clinical (a and b) and dermoscopic (c) appearance of a large, traumatized SK. (a) Overview of the trunk of an 80-year-old man, with a large brown to black plaque with a hypopigmented central area. (b) Close-up of the lesion, with a dark elevated border and a central white area. (c) Dermoscopy, showing well-demarcated borders, multiple milia-like cysts, and comedo-like openings. Small, black dots are also detected, most probably representing melanin deposition. No features of a melanocytic lesion are detected.

There is no pigment network, but small foci of network-like structures may be evident at the periphery of lesions. The lines of these structures are often hyperpigmented and may end abruptly at the periphery. The grids of these network-like structures are much larger than the one seen in a typical pigment network, and the holes do not always correspond to the tips of the dermal papillae, but to keratin-filled structures (fissures and comedo-like openings). Sometimes a vascular pattern exhibiting hairpin vessels and dotted vessels can be appreciated. They correspond to long capillary loops, commonly seen in keratinizing tumors, and are mainly found at the border or in the periphery of the lesions.

In evolving acanthotic SK, sometimes the global pattern resembles the surface of the brain, and the underlying dermoscopic structures are therefore called gyri and sulci. Histologically, they correspond to rounded protrusions of the acanthotic epidermis and papillary dermis (gyrus) surrounded on each side by furrows (sulci) filled with keratinous material. The yellowish to light brownish lines between gyri are called sulci or fissures and are arranged reciprocal to the gyri, thus giving rise to the peculiar “brain-like” appearance (Figure 13.4).

Sometimes the brain-like appearance is not recognizable, and one can find the presence of the so-called “fat fingers.” They are thick, digitate linear, curvilinear, branched, or oval or circular dermoscopic structures that represent the gyri of the cerebriform surfaces.

Reticulated type

The reticulated type of SK is characterized by a reticulated pattern. On the face, it is combined with the site-specific pseudonetwork. This frequently causes diagnostic difficulties in the differentiation from melanoma in situ on severely sun-damaged skin (lentigo maligna).

In such cases, the presence of a moth-eaten border of the so-called jelly sign and the presence of a pigment appearing as a smear can be helpful for diagnosis. A type of “network” that may be seen in an SL or an early SK is “fingerprinting.” These are networks that are light brown and delicate, and have a fingerprint pattern.

Verrucous type

The verrucous type of SK has an unspecific dermoscopic pattern. Because of the exaggerated orthohyperkeratosis, local features are not visible, and therefore the dermoscopic examination only reveals whitish to yellowish horn masses.

Clonal SK

Clonal (nesting) SKs are characterized histopathologically by the presence of nests of cells that differ morphologically from their neighbors within the background of an SK. Dermoscopic examination can reveal large areas of a bluish pigmentation composed of multiple, variously sized, and irregularly distributed blue-gray roundish structures, also aggregated to form short lines. The blue-gray structures are similar to the so-called blue-gray ovoid

nests, which are a dermoscopic hallmark of pigmented BCC. Dermoscopy does not reach 100% diagnostic accuracy, and clonal SK may represent a dermoscopic pitfall, being difficult to differentiate from melanoma and BCC. Histopathologic examination should always be performed in cases in which dermoscopy reveals confounding features that do not allow an accurate diagnosis (Figure 13.6).

Melanoacanthoma

The melanoacanthoma variant presents a pronounced black pigmentation that is usually camouflaging the pathognomonic local features, thus rendering these lesions difficult to differentiate from pigmented Spitz nevi and melanoma.

Lichen planus–like keratosis

Lichenoid keratosis, or LPLK, has been proposed to represent a regressive epidermal lesion, either an SL or an SK. At the end of the regressive process, LPLKs usually dermoscopically show a diffused granular pattern, characterized by the presence of scattered grayish dots. Remnants of the preexisting lesion are detected in typical lesions. When only the latter granules and no additional clues are visible, an accurate differential diagnosis between LPLK and regressive melanoma is virtually impossible, and the lesions have to be excised for histologic diagnosis.

Irritated SK

Irritation can be responsible for the presence of variously sized and shaped scale crusts, and atypical vasculature, thus masking the diagnostic features. Anti-inflammatory treatment for a few weeks is sometimes sufficient to clarify the correct diagnosis.

PIGMENTED BASAL CELL CARCINOMA

BCC is an epithelial tumor that arises from basal cells. The prognosis for patients with BCC is excellent in the majority of cases; metastases are exceedingly rare (0.028%–0.55%). However, if the disease is allowed to progress, it can cause significant morbidity.^{28,29} BCC is the most common skin cancer in humans. It occurs predominantly on the head, with 70% of BCCs occurring on the head (most frequently on the face), 25% on the trunk, and 5% on other areas.^{28,29} The exact cause of BCC is unknown; however, environmental and genetic factors can predispose patients to BCC.

Environmental factors include sunlight. Particularly, chronic exposure is the most frequent association with the development of BCC. Radiation exposure that contributes to BCC development may include tanning booths and UV light therapy. X-ray and grenz ray exposure are associated with BCC formation.

Genetic involvement has been demonstrated on chromosome 9 in patients with familial basal cell nevus syndrome (Gorlin syndrome). Such mutation involves the patched (PTCH) gene, a tumor suppressor gene. Inappropriate activation of the hedgehog signaling pathway is found in both sporadic and familial cases of BCC. This results in loss-of-function mutations in tumor suppressor protein

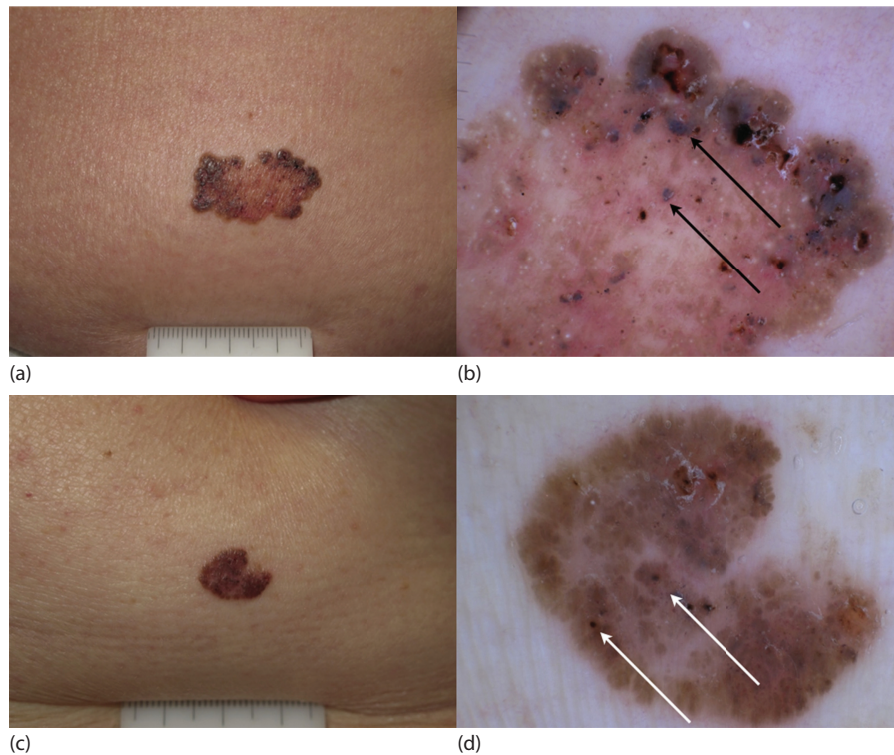


Figure 13.6 Striking similarity of clonal SK (a and b) and pigmented BCC (c and d). (a) Clinical appearance of a large pigmented plaque arising on the abdomen of a 65-year-old woman. (b) In dermoscopy, the lesion shows well-demarcated borders, a reddish central area, multiple milium-like cysts, and multiple roundish blue structures (black arrows). (c) Clinical image of a pigmented plaque, arising on the back of a 77-year-old man. (d) On dermoscopy, maple leaf-like areas are detected at the border of the lesion and concentric structures are centrally seen (white arrows).

patched homologue 1 (PTCH1) and gain-of-function mutations in sonic hedgehog (SHH), smoothened (SMO), and Gli.^{30,31}

Patients with XP, an autosomal recessive disease, may develop BCC, SCC, and malignant melanoma starting from early childhood.⁸

Nevoid basal cell carcinoma syndrome

This is an autosomal dominant disorder that can result in the early formation of multiple odontogenic keratocysts, palmoplantar pitting, intracranial calcification, and rib anomalies. Various tumors, such as medulloblastomas, meningiomas, fetal rhabdomyomas, and ameloblastomas, also can occur.^{32–34} Mutations in the hedgehog signaling pathway, particularly the patched gene, are causative.

Bazex syndrome

Features of Bazex syndrome include follicular atrophoderma (so-called ice pick marks, especially on dorsal hands), multiple BCCs, and local anhidrosis (decreased or absent sweating).³⁵

Histopathology

Several histologic types of BCC exist. Usually, BCCs are well differentiated and cells appear histologically similar to basal cells of the epidermis.

Tumor cells of nodular BCC, sometimes called basalioma cells, typically have large, hyperchromatic, oval nuclei and little cytoplasm. Nodular tumor aggregates may be of varying sizes, but tumor cells tend to align in a palisade pattern at the periphery of these nests. Cleft formation commonly occurs between BCC nests and stroma. Increased mucin is often present in the surrounding dermal stroma.

In pigmented BCC, benign melanocytes in and around the tumor produce large amounts of melanin. These melanocytes contain many melanin granules in their cytoplasm and dendrites.

Clinical presentation

The clinical presentation of BCC varies by type. Patients often report a slowly enlarging lesion that does not heal and that bleeds when traumatized. Physical examination of the skin aids in determination of tumor extent, subtype, and involvement of important cosmetic and functional structures. Several clinicopathologic types of BCC exist, each of which has a distinct biologic behavior. However, considering only pigmented BCC, the nodular and superficial subtypes are taken into account. Infiltrative, morpheaform, and micronodular BCC usually present as nonpigmented tumors.

Nodular is the most common type of BCC. It usually presents as a round, pearly, flesh-colored papule with

telangiectasia and a variable amount of blue, brown, and black pigmentation.

The superficial type is seen mostly on the upper trunk or shoulders. It appears clinically as an erythematous, well-circumscribed patch or plaque, often with superficial erosions and a variable amount of brown, black, and gray pigmentation.

Dermoscopy

In addition to the well-known value of dermoscopy in the diagnosis of BCC, recent research highlighted the value of dermoscopic imaging in influencing the management decision when dealing with BCCs. In summary, indications for dermoscopy are (1) predicting the histopathologic subtype and (2) assessing the presence of pigmentation.^{36–47} Moreover, a dermoscopic signature pattern has been noticed, meaning that patients' characteristics, such as skin type, may influence the clinical and dermoscopic appearance of BCC (Figures 13.7 through 13.10).⁴⁷

Pigmented nodular BCC is dermoscopically typified by blue-gray ovoid nests or multiple blue-gray dots or globules, usually associated with arborizing vessels and/or ulceration.

Pigmented superficial BCC shows light brown to grayish concentric structures, spoke wheel areas, or maple leaf-like areas. Instead, detection of blue-gray ovoid nests signifies the presence of dermal pigmented basoid nests, indicating that the tumor is not superficial.

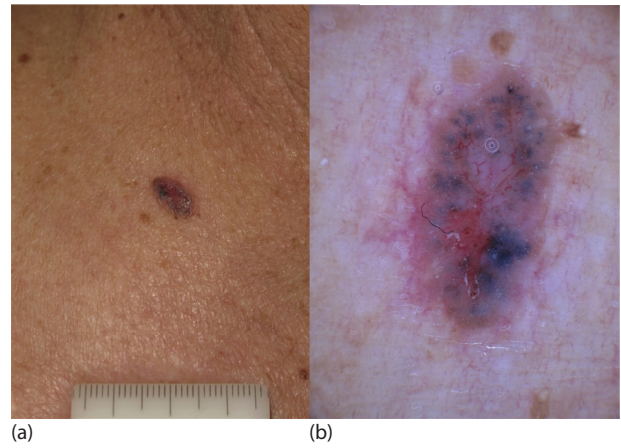


Figure 13.8 Nodular pigmented BCC. (a) Clinical appearance of an ulcerated pigmented BCC. (b) Under dermoscopy, multiple blue ovoid nests are visible, over a pinkish background, with central ulceration and multiple thin teleangectasias.

Multiple erosions and short fine teleangectasias can be variably present.

In the following, we present a summary of the most common BCC criteria. *Blue-gray ovoid nests* are well-circumscribed, confluent pigmented ovoid or elongated configurations, larger than globules and not intimately connected

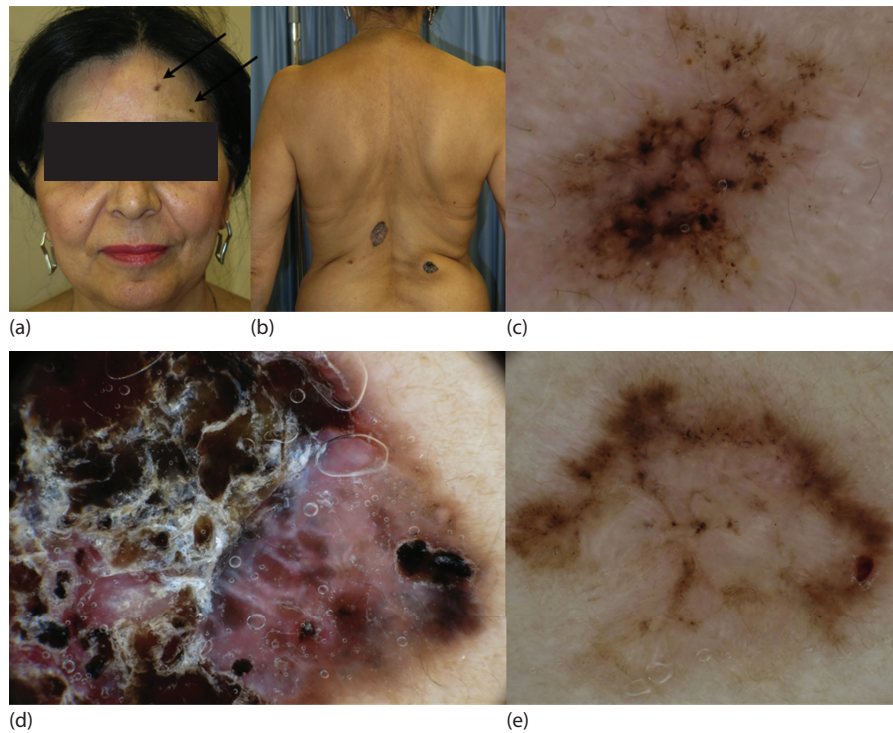


Figure 13.7 Clinical (a and b) and dermoscopy (c–e) images of multiple pigmented BCCs. (a) Two pigmented macules on the face of a 55-year-old woman with skin type IV. (b) Three pigmented plaques on the back of the woman. (c) Superficial pigmented BCC, displaying peripheral leaflike areas and multiple gray to black dots and globules. (d) Nodular pigmented BCC, with a hyperkeratotic surface and multiple ovoid nests. (e) Superficial BCC, showing a white structureless area and maple leaf-like areas, seen as brown to blue-gray peripheral bulbous extensions. A few small gray dots are also detected.

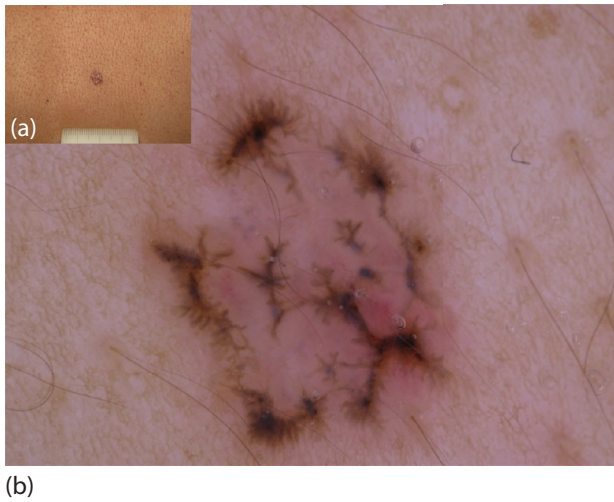


Figure 13.9 Superficial pigmented BCC. (a) Clinical close-up of a pigmented macule, with translucent borders, arising on the back of a 45-year-old woman. (b) Dermoscopy showing multiple leaflike areas, a structureless central area, and multiple blue-gray globules.

to a pigmented tumor body. Microscopically, they correspond to large well-defined tumor nests with pigment aggregates, invading the dermis. Blue-gray ovoid nests can be seen in all subtypes except for superficial BCC. *Multiple blue-gray dots and globules* are numerous, loosely arranged, round to oval well-circumscribed structures, which are smaller than the

nests. Their histopathologic correlates are small, roundish tumor nests with central pigmentation, localized to the papillary dermis and/or reticular dermis. Multiple blue-gray dots and globules can be seen in all BCC subtypes.

In-focus dots are loosely arranged well-defined small gray dots, which appear sharply in focus. Histopathologically, they correspond to free pigment deposition along the dermoepidermal junction and/or melanophages in the papillary and reticular dermis.

Ulceration may be seen as one or more large structureless areas of red to black-red color. At the sites of ulceration, histopathology shows loss of the epidermis, usually covered by hematogenous crusts. Ulceration typically characterizes nodular tumors.

Maple leaf-like areas are translucent brown to blue-gray peripheral bulbous extensions that never arise from the pigmented network or from adjacent confluent pigmented areas. In histopathology, they correlate to multifocal tumor nests containing pigment aggregates, connected to each other by lobular extensions. They are mainly localized in the epidermis and less frequently in the papillary dermis. Maple leaf-like areas represent a highly specific BCC feature and can be seen in all subtypes, but more frequently in superficial BCC.

Spoke wheel areas are well-circumscribed radial projections, usually tan but sometimes blue or gray, meeting at an often darker (dark brown, black, or blue) central axis. Histopathologically, they correspond to tumor nests arising and connected to the epidermis, characterized by finger-like

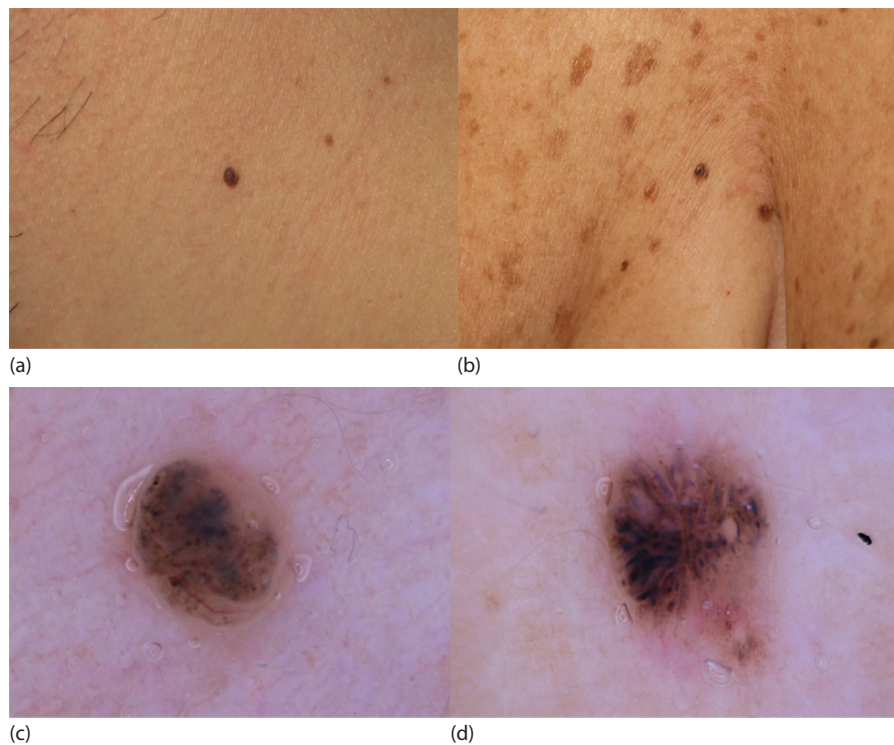


Figure 13.10 Nevoid BCCs. Clinical (a and b) appearance of two pigmented papules on the back of a 35-year-old woman affected by Gorlin syndrome (basal cell nevus syndrome). The lesions have a shiny surface. In dermoscopy (c and d), a brown background coloration is seen, with multiple blue-gray globules.

projections and centrally located pigmentation. Spoke wheel areas represent a highly specific BCC feature and can be seen in all subtypes, but more frequently in superficial BCC.

Concentric structures are defined as irregularly shaped globular-like structures with different colors (blue, gray, brown, and black) and a darker central area, which possibly represent variations or “precursors” of the spoke wheel areas. They can be seen in all subtypes, but more frequently in superficial BCC.

Arborizing vessels are large-diameter vessels, branching irregularly into the finest terminal capillaries. Their color is bright red, being perfectly in focus due to their location on the surface of the tumor (just below the epidermis). Histopathologically, arborizing vessels correspond to dilated vessels in the dermis.

Superficial fine telangiectasias (SFTs) are defined as short, fine, focused linear vessels with very few branches. Their histopathologic correlation is telangiectatic vessels located in the papillary dermis. SFTs typically characterize superficial BCC.

Multiple small erosions are usually seen as small brown-red to brown-yellow crusts. They histopathologically correspond to thin crusts overlying superficial loss of the epidermis and are associated with superficial BCC.

Shiny white-red structureless areas have been described mainly in the context of superficial BCC and may represent diffuse dermal fibrosis or fibrotic tumoral stroma.

Short white streaks (chrysalis) can be seen only with polarized dermoscopy as orthogonal short and thick crossing lines. They may be attributed to the presence of collagenous stroma and fibrosis in the dermis.

A peculiar dermoscopic subtype of BCC has been described in Gorlin syndrome, named nevoid BCC. These lesions clinically resemble skin tags or dermal nevi. In dermoscopy, a brown background pigmentation is detected, together with multiple blue-gray dots and globules.

PIGMENTED ACTINIC KERATOSIS

AKs are the most common lesions within the spectrum of keratinocyte skin cancer. The premalignant nature of AK is well recognized, although it is impossible to predict which individual lesion will follow which course, as most patients have many lesions. The typical patient with AKs is an elderly, fair-skinned, sun-sensitive person. The lesions arise in areas of long-term sun exposure, including the face, ears, and in men, bald scalp, as well as in the dorsal forearms and hands. Patients may develop multiple lesions within a single anatomic area and produce confluent AK over a relatively large area.^{48–52}

Clinical presentation

They typically present as pink to red macules, with a variably scaly surface. Less frequently, AKs may present a clinically visible pigmentation, pigmented AK (PAK). PAK can be difficult to differentiate from other pigmented lesions, such as melanoma and lentigo maligna melanoma, SL, early SK, and LPLK. In the context of actinically damaged skin, characterized by the presence of mottled

pigmentation, discriminating between benign macules and pigmented tumors may be challenging; thus, histopathologic confirmation is frequently required in the diagnosis of PAK in order to exclude melanoma.

Histopathology

PAK is characterized by a variable degree of keratinocyte atypia, from sparse atypical basal keratinocytes to full-thickness dysplasia, and an increase melanin deposits, keratinocytes and melanocytes, and/or dermal melanophages. A parakeratotic scale is often present.

Dermoscopy

Dermoscopy features of PAK have been described recently.^{53–58} The majority of lesions are located on the face; however, they can arise everywhere on chronically sun-damaged skin. The most characteristic dermoscopic feature of PAK is a superficial brown to gray network consisting of brown, curved double lines that surround enlarged, partially confluent, keratotic follicles of various sizes. A red pseudonetwork and scales can sometimes be also seen. In addition, PAK may exhibit overlapping features with early-phase lentigo maligna (LM), including gray dots (annular granular pattern), gray-brown lines (pseudonetwork or rhomboidal structures) around the follicular openings, and asymmetrical, pigmented follicular openings. Indubitably, PAKs represent a pitfall in the dermoscopic differential diagnosis of melanoma, since almost all dermoscopic findings of LM can be also seen in PAK. In a recent study, dermoscopy clues to differentiate between PAK and LM were analyzed. White and evident follicles, scales, and red color represented significant diagnostic clues for PAK. Instead, intense pigmentation and gray rhomboidal lines appeared highly suggestive of LM (Figures 13.11 and 13.12).

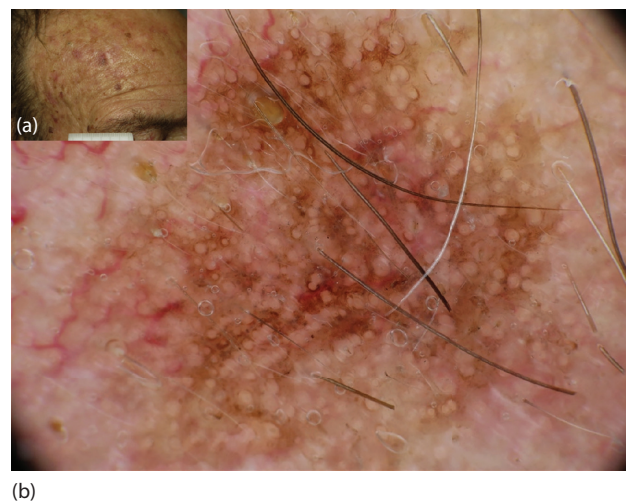


Figure 13.11 PAK. (a) Scaly, pigmented macule on the forehead of a 76-year-old man. (b) In dermoscopy, a superficial brown to gray network is seen consisting of brown, curved double lines that surround enlarged, partially confluent keratotic follicles of various sizes.

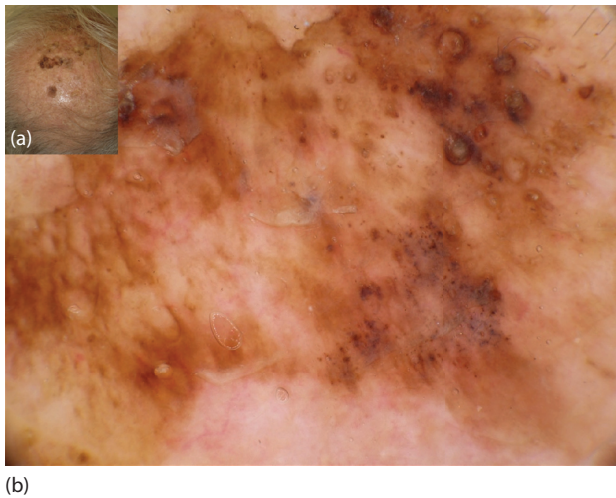


Figure 13.12 PAK. (a) A pigmented macule on the scalp of an 80-year-old man. (b) In dermoscopy, the lesion presents with moth-eaten borders, a scaly surface, and structureless pigmentation, varying from light to dark brown.

PIGMENTED SQUAMOUS CELL CARCINOMA

Cutaneous SCC is the second most common skin cancer, after BCC.⁵⁹ Although SCC is not often fatal, many of these lesions occur in the head and neck region, where surgery for advanced-stage disease can be disfiguring. Despite increased knowledge and public education regarding the causes of skin cancer and prevention strategies, the incidence of SCC continues to rise worldwide. This increasing incidence is likely multifactorial. Speculated causes include an aging population, improved detection, increased use of tanning beds, and environmental factors. Additionally, the number of patients on immunosuppressive therapy, used in solid organ transplantation and various rheumatologic and dermatologic conditions, is increasing. Solid organ transplant recipients have a markedly elevated risk of SCC formation. Metastasis may also be more common in this group.⁶⁰

Clinical presentation

The classic presentation of an SCC is that of a superficial ulcer with heaped-up edges, often covered by a plaque, usually in a sun-exposed area. Typical surface changes may include scaling, ulceration, crusting, and cutaneous horn. More rarely, the lesion can be pigmented.⁶¹

Squamous cell carcinoma in situ (CIS), sometimes referred to as Bowen's disease, is a precursor to invasive SCC.

Histopathology

Characteristics of squamous cell CIS include nuclear atypia, frequent mitoses, cellular pleomorphism, parakeratosis and hyperkeratosis, and a disorganized progression of cells from the basal to apical layers of the epidermis. CIS is differentiated from AK, a similar precancerous skin lesion, by the full-thickness involvement of the epidermis in CIS.

Invasive cutaneous SCC (cSCC) is differentiated from CIS and AK by the invasion of the basement membrane by malignant-appearing cells. With invasive cSCC, nests of atypical cells are found within the dermis, surrounded by an inflammatory infiltrate.

Dermoscopy

Pigmented intraepidermal carcinoma

Pigmented Bowen's disease may dermoscopically reveal several pigmented structures, including structureless brown to gray areas; brown dots; thick, pigmented lines; or a combination of these patterns. Dotted and/or glomerular vessels, usually combined with white to yellow surface scales and a red-yellowish background color, can be present. Interestingly, a linear arrangement of dots or vessels at the periphery of the lesion has been suggested to represent a relatively specific dermoscopic sign of Bowen's disease (Figure 13.13).^{62–66}

Dermoscopy of invasive squamous cell carcinoma

Invasive SCC may dermoscopically display several different morphologic types of vessels, including peripheral hairpin, dotted, and/or linear irregular vessels. In addition, the detection of signs of keratinization significantly facilitates the recognition of the tumor. These signs of keratinization include amorphous, structureless white to yellow areas or targetoid-appearing follicular openings consisting of an opaque, yellow center surrounded by a white halo (white circles). Dermoscopy of pigmented SCC has been described only in few cases, due to the rarity of the disease. In addition to the common dermoscopic features of SCC, a blue to black background structureless pigmentation can be detected in these cases, which may represent a pitfall in the differential diagnosis with melanoma (Figure 13.14).^{61,67–69}

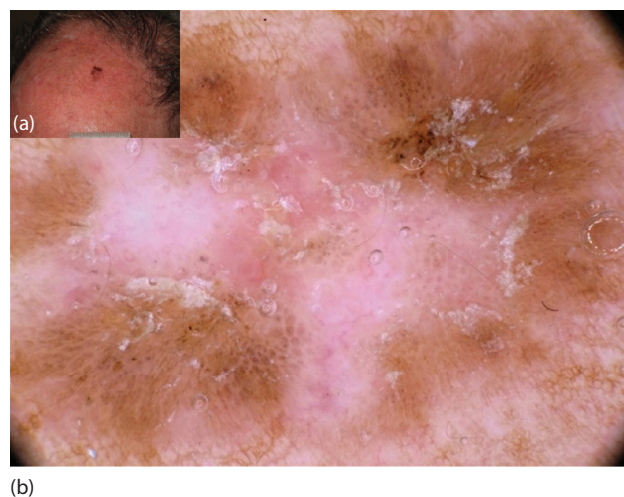


Figure 13.13 Pigmented Bowen's disease. (a) Pigmented macule on the forehead of a 76-year-old man with sun-damaged skin. (b) In dermoscopy, a structureless white central area is detected. Multiple brown globules in a line are seen at the periphery of the lesion.

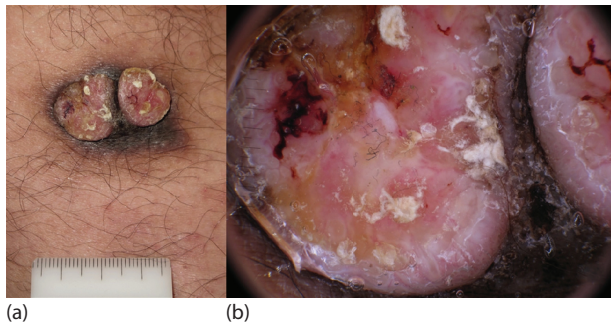


Figure 13.14 Pigmented SCC. (a) A hyperkeratotic nodule located on the posterior aspect of the leg of a 45-year-old man. (b) Dermoscopy showing an ulcerated nodule, with a keratotic surface, and heavily pigmented skin at the base of the nodule.

DERMATOFIBROMA

DF (superficial benign fibrous histiocytoma) is a common cutaneous lesion, usually a nodule, of unknown etiology. The precise mechanism for the development of DF is unknown. It has been considered a reactive tissue change; however, evidence that DF may be a neoplastic process is demonstrated by its clonal proliferative growth.

DF frequently develops on the extremities (mostly the lower legs) and is usually asymptomatic, although pruritus and tenderness can be present. It is actually the most common painful skin tumor.^{69,70}

Clinical presentation

Clinically, DFs appear as firm, single, or multiple hard papules, plaques, or nodules, with a smooth surface, usually characterized by a color variable from light brown to dark brown, purple-red, or yellow. DF can develop anywhere on the body surface, with a predilection for the lower extremities.

Histopathology

Histologically, it can be defined as a fibrosing cutaneous lesion characterized by an increased number of fibrocytes in the dermis and occasionally subcutis, and a variable admixture of macrophages and other inflammatory cells, with coarse collagen bundles and hyperplasia of adjacent structures (epidermis and hair follicles) or cells (melanocytes).

Dermoscopy

Although the clinical diagnosis of DF is rather easy, in some instances the differentiation from other tumors, such as melanoma, is difficult. The most frequent dermoscopic presentation that we can describe as classical DF includes the presence of a peripheral delicate pigment network and central white scar-like patch. Palpation is of diagnostic relevance in the diagnosis of DF. This fact should be kept in mind when judging only the dermoscopic image of a given DF.

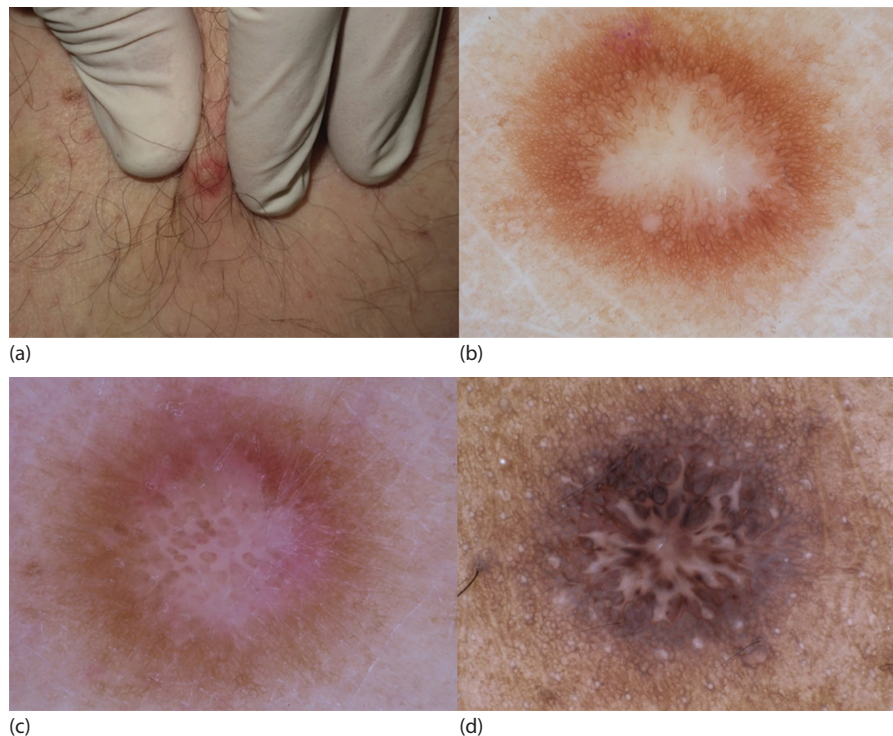


Figure 13.15 Many faces of DFs. (a) Clinical appearance of a firm nodule on the leg of a 40-year-old woman. (b) Stereotypical appearance of DF in dermoscopy, with a central white patch and thin brown network in the periphery. (c) Dermoscopy of a DF, showing a central white patch, thin network in the periphery, and multiple globular-like structures in the center. (d) Dermoscopy of a heavily pigmented DF.

Several patterns were identified and recently described.^{71–73} These patterns can be grouped into two main groups:

1. DFs with a peripheral delicate pigment network
2. Those without the peripheral pigment network

In summary, we can recognize 10 different dermoscopic patterns.⁷³

● First group:

- Pigment network located throughout the lesion
- Delicate pigment network at the periphery and central white scar-like patch
- Delicate pigment network at the periphery and central white network
- Delicate pigment network at the periphery and central homogeneous pigmentation

● Second group:

- White network throughout the lesion
- Homogeneous pigmentation throughout the lesion
- Total scar-like patch and a variant with multiple white scar-like patches regularly distributed
- Peripheral homogeneous pigmentation and central white scar-like patch
- Peripheral homogeneous pigmentation and central white network
- Atypical pattern that consists of the presence of an atypical pigment network, an atypical scar-like patch or white network, an atypical homogeneous pigmentation, or the irregular distribution of these structures

Vascular structures in DFs can be frequently observed, and may represent a confounding feature. They include dotted and hairpin vessels in the center of the lesion or throughout the entire lesion, telangiectasia in the center of the lesion, and polymorphous, atypical vessels. Additional dermoscopic patterns include globular-like structures and a rainbow pattern (Figure 13.15).

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INTRODUCTION

Any unintended harmful reaction to a medicine or drug is known as an adverse drug reaction (ADR) according to the definition by the World Health Organization.^{1,2}

Skin pigmentation may be induced by skin diseases, specific conditions, and a wide variety of drugs. Drug-induced hyperpigmentation is a predictable side effect and is related to the pharmacologic action of the drug; hence, this type of reaction is considered nonimmunologic. Many drugs induce hypermelanosis as a nonspecific postinflammatory change in predisposed subjects, and it occurs in different skin levels.

The true incidence of these pigmentary changes is very difficult to assess. Not all cases are recorded and declared to the pharmacological survey or drug institutions. No large-scale prospective studies have been performed so far, and diagnosis is not always properly established because of a lack of direct evidence and lack of full and adequate information provided by the patients about their treatment, doses, duration, etc.

Pigmentation disorders include a large number of heterogeneous conditions that are usually characterized by altered melanocyte density, melanin concentration, or both, and result in altered pigmentation of the skin. Some of these disorders are extremely common (melasma and vitiligo), whereas others are rare. In this contribution, we review the most common pigmentation disorders that appear on the face. These lesions, even though mostly asymptomatic, have a great impact on a patient's quality of life.

Numerous medications have been implicated in the appearance of dark lesions on the skin. There is little evidence for drug-induced hyperpigmentation. The level of evidence supporting a causal relationship between hyperpigmentation and medication use varies considerably. A causal relationship appears likely only for a limited number of drugs.³

Drug-induced pigmentation represents 10%–20% of all cases of acquired hyperpigmentation, and this hypothesis must be systematically raised in unexplained pigmented lesions, especially in elderly people. Drug-induced pigmentation is often worsened by sun exposure either by direct stimulation of melanin synthesis or by transformation of the drug to visible particles.

Drug-induced hyperpigmentation may be caused by dermal and epidermal deposition of drug metabolites, hemosiderin, melanin, or a combination of pigment types.⁴

PATHOGENESIS

The accurate pathogenesis of drug-induced hyperpigmentation is not fully understood. The pathogenetical mechanisms of drug-induced pigmentation are variable according to the causative medication and can involve an accumulation of melanin. Sometimes following a non-specific cutaneous inflammation (any type of skin rash) and often worsened by sun exposure, an accumulation of the triggering drug itself, a synthesis of special pigments under the direct influence of the drug or deposits of iron following damage to the dermal vessels.

Pathogenetic mechanisms include the following:

1. Accumulation of melanin following a nonspecific cutaneous inflammation and often worsened by sun exposure. This accumulation of melanin usually results either from hyperproduction by epidermal melanocytes or in response to a nonspecific cutaneous inflammation.
2. Hyperpigmentation results from the accumulation of the triggering agent itself.
3. Some drugs synthesize special pigments, such as lipofuscin, probably under the direct influence of the drug deposition of iron in the dermis following damage to dermal vessels. This usually results from drug-induced damage of dermal vessels with leakage of red blood cells.⁵

It has been suggested that antimalarials have an affinity for melanin and can accumulate within the skin.

These mechanisms are certainly not the only ones to explain drug-induced dyschromia, but they seem to encompass the majority of the involved mechanisms, as demonstrated by physical and chemical investigations.

Drugs can cause hyperproduction of melanin by stimulating epidermal melanocytes, either directly or indirectly, through a nonspecific cutaneous inflammation.

They may also impair melanin clearance from dermal macrophages by binding to melanin and creating a stable complex.

The accumulated melanin is found either free in the dermis or within dermal macrophages.

Apart from the accumulation of melanin, other mechanisms responsible for drug-induced dark lesions include the accumulation of the triggering medication itself, the synthesis of special pigments under the influence of the drug, and the deposition of iron from drug-induced damage to dermal vessels.⁴

One possible underlying mechanism in hyperpigmentation is the stimulation of melanogenesis due to increased

secretion of the melanocyte-stimulating hormone (MSH), melanotropin. The association between smoking and oral hyperpigmentation is probably based on direct stimulation of melanocytes due to nicotine and possibly benzpyrene.⁶

The level of evidence supporting a causal relationship between hyperpigmentation and medication use varies considerably. Most of the evidence comes from case studies on individual or repeated observations. Systematic studies are rarely found in the literature. The evidence on drug-induced hyperpigmentation is poor. Most reports on a relationship between the use of a drug and hyperpigmentation are based on individual patient cases, and do not prove a clear casual relationship. This also applies to drugs for which pathophysiological mechanisms would make causality seem plausible, for example, antibiotics and psycholeptics. For the numerous reports on hyperpigmentation occurring after antineoplastic drug use, the literature offers no possible interpretations.⁷

Pigment abnormalities are particularly common among patients taking *phenothiazines*. A total of 1.7% of 768 hospitalized schizophrenic patients were found to have skin pigment abnormalities.⁸

Chlorpromazine and, less commonly, other phenothiazines cause a tan, blue-grey, or slate-grey pigmentation that is particularly prominent on sun-exposed surfaces, as well as pigment deposits in the lens and cornea.⁹⁻¹⁸

Studies with a high evidence level were found for prostaglandin agonists, which are used to treat intraocular pressure. These included findings from placebo-controlled clinical studies; hyperpigmentation of the iris, eyelids, eyelashes, and periorbital skin were reported as adverse effects related to drug use. The number of patients with hyperpigmentation was larger in the treatment groups than in the respective placebo group. A pathogenetic explanation was also offered: prostaglandin F_{2α} stimulates the activity of tyrosinase. Prostaglandins increase the dendritic structure of melanocytes and melanin synthesis. The hyperpigmentation resolved after stopping the drug.¹⁹

CLINICAL MANIFESTATION AND COURSE

Clinical features are very variable according to the triggering molecule, with a large range of patterns and shades that are sometimes more or less reminiscent of the culprit drug.

Drug-induced hyperpigmentation cannot be considered specific, but some peculiarities may draw the examiner's attention. The discoloration acquired usually has a slow onset and progresses very gradually over months or even years after the initiation of the drug. Apart from the usual brownish coloration that we observe in most facial hypermelanoses, drug-induced hyperpigmentation may also have a blue-grey hue.

Topographic distribution and sun-exposed areas, as well as mucous membranes (mouth and conjunctivae), are favorite sites and types for the lesions, and sun exposure usually aggravates them. Other lesions, such as inflammatory or lichenoid rashes, may accompany the drug-induced hyperpigmentation, which usually fades, although not

always completely, when the responsible medication is discontinued.

Skin elements may worsen at each recurrence when the patient is rechallenged with the triggering drug. They may be single or multiple, and the diagnosis is based on medical history of recurrent erythematous, eczematous, or occasionally even bullous lesions following the intake of a particular medication.

Note that the low-grade photosensitivity disappears 12–24 months after the drug is discontinued; the long period results from the gradual elimination of the photoactive drug from the lysosomal membranes. The pigmentation also disappears after 1–3 years if the drug is discontinued and sun is avoided.

Main drugs implicated in causing skin pigmentation

Tetracycline and tetracycline group

Tetracycline-induced pigmentary changes²⁰ have been mainly reported with minocycline, and much less frequently with doxycycline or first-generation molecules.^{21,22}

Since its introduction in the early 1970s, minocycline, a second-generation tetracycline, has been used for a variety of infectious diseases of respiratory tract infections, STDs, and acne. Minocycline is one of the drugs currently being evaluated as a neuroprotective agent. The anti-inflammatory properties of minocycline have enabled it to be effective in many inflammatory diseases, including pyoderma gangrenosum, autoimmune bullous dermatoses, and acne.²³

Risk factors for the development of tetracycline-induced hyperpigmentation are

- Duration of treatment
- Cumulative dose (high risk above 50 g)
- Possibility of occurring after a smaller dose
- Presence of previous skin alterations related to inflammation
- Excessive sun exposure
- Concomitant intake of other pigmentation-inducing medications

Minocycline-induced hyperpigmentation (MIH) may occur in up to 15% of patients receiving this antibacterial, especially in long-duration treatments, but the overall incidence is usually estimated to be between 3% and 5%.²⁴⁻²⁹

MIH may cause discoloration of the skin, nails, conjunctiva, sclera, oral mucosa, bone, and teeth.^{30,31}

The data on hyperpigmentation after minocycline use³² are also better, although it is uncertain whether increased melanin is the cause. Although the number of prescriptions for minocycline were estimated by the manufacturer in 1985 to be 55 million doses, until then there were no systematic observations of pigmentation, and only 77 such events were reported to the manufacturer. Most studies on minocycline report on individual case observations. The first report on MIH was published in 1970. Pigmentation occurred after 20 days of treatment at a dosage of

400 mg daily; it gradually disappeared after treatment was discontinued.³²

Minocycline and tetracycline hyperpigmentation is not always the result of increased melanin. Of the four types of hyperpigmentation,

- *Type 1:* Blue-black hyperpigmentation at the site of prior inflammation or scarring. Caused by pigment granules, which are probably iron chelates of minocycline.
- *Type 2:* Blue-gray hyperpigmentation affecting normal skin, mainly on the legs. Probably due to metabolites of minocycline in the skin. The black pigment appears to correspond to a colored quinone, which is derived from the aromatic ring.
- *Type 3:* Dirty skin syndrome on sun-exposed areas. Microscopic studies have found increased amounts of melanin in the epidermis and dermal macrophages.³³
- *Type 4:* Hyperpigmentation of scars.³⁴

In general, MIH may have the appearance of localized or diffuse hyperpigmented blue-gray or slate-gray macules on the anterior sides of the lower legs or other sun-exposed areas: ankles, dorsa of the feet, face (especially around the eyes), sites of trauma, sites of inflammation (acne scars, contusions, and abrasions), and other sites, such as teeth and nails.

The fact that pigmentation is more commonly related to minocycline treatment than that of other tetracyclines probably has to do with the treatment duration and total dosage, e.g., in acne.³⁵

The cutaneous pigmentation is a result of an interaction between the drug metabolite and metal ions and/or melanin. An iron-containing brown pigment, not melanin, is located in the dermal macrophages.

Retrovirals

Hyperpigmentation in AIDS patients may occur as a complication of drug therapy, most notably with zidovudine, which causes brown macular pigmentation on the lips or oral mucosa, and longitudinal brown lines on the nails, skin, and oral mucosa.

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs)³⁶ are a potential source of depigmentation. The manifest with fixed drug eruption (round or oval, sharply demarcated erythematous plaques on the lip, hip, sacrum, or genitalia).

Pigmentation is most commonly associated with oxycam derivatives, acetaminophen (paracetamol), dapsone, salicylates, antipyrine, aminopyrine, or oxyphenbutazone, but has also been reported with many other medications, as well as, for example, sulfonamides, barbiturates, and phenacetin.

Antimalarials

Antimalarial (amodiaquine, hydroxychloroquine, quinacrine, and chloroquine)³⁷ hyperpigmentation (dark purple to bluish gray) occurs mainly on the anterior side of the legs, head (cheeks, forehead, ears, and nose), nail

bed (transversal bands or diffuse pigmentation), and mucosa—predominantly on sun-exposed areas. It occurs in 25% of individuals who take the drug for longer than 4 months. The main drugs are chloroquine, hydroxychloroquine, mepacrine (quinacrine), and mefloquine. With quinacrine, pigmentation is yellow-green or yellow due to quinacrine-containing complexes. Discoloration disappears within a few months of the drug being discontinued.

Hyperpigmentation is certainly the most frequently reported and one of the most impressive cutaneous adverse effects of this category of drugs.^{37–41} In regard to antimalarial drugs, increased levels of melanin and hemosiderin have been found in hyperpigmented areas.⁴² Cutaneous side effects of antimalarial therapy also include pruritus, xerosis, exacerbation of preexisting psoriasis, hair discoloration, urticarial and lichenoid skin rashes, and Stevens–Johnson syndrome.

Antiarrhythmics

The antiarrhythmic and coronary vasodilator amiodarone⁴³ has long been known to induce a distinctive blue-gray or purple discoloration of sun-exposed areas, especially the face, with prominent involvement of the nose and sometimes the ears.⁴⁴

It causes blue-gray or purple discoloration on sun-exposed skin. Yellow-brown corneal pigmentation is often associated with skin changes and may occur very early in treatment, whereas hyperpigmentation usually appears after 6 months of therapy.

The risk of developing pigmentary changes during an amiodarone treatment course includes daily dosage and duration of treatment (high risk with dosage more than 800 mg/day).

Pigmentation is usually, although slowly, reversible after discontinuation of the medication, but lesions may persist for up to 1 year, or even longer.

Cytotoxic drugs

Cytotoxic drugs⁷ could affect all parts of the tegument, including the hair, nails, and mucous membranes; be either diffuse or localized; and sometimes have a distinctive pattern. Hyperpigmentation is a very common adverse effect of chemotherapeutic agents used in cancer treatment. Pigmentation appears or predominates on areas of chronic or acute trauma. The skin pigmentation may take several different topographical patterns.

The pigmentation usually fades, at least partially, when the inducing agent is stopped, but it may persist for a long time after the treatment is discontinued, as is the case with bleomycin. In rare cases, the lesions are permanent.

The pathogenesis includes a direct toxic effect on melanocytes with subsequent melanin synthesis stimulation; the hypersecretion of corticotropin (adrenocorticotrophic hormone [ACTH]) and MSH as a result of adrenal toxicity; a deficiency in tyrosinase inhibitors; the formation of stable drug–melanin complexes; and postinflammatory pigmentation following toxicity affecting keratinocytes with or without photosensitivity.

Discoloration may occur after a very variable interval of time following the start of treatment, depending on the drug in question, and may range from 1 week to several months.

- **Concurrent neoadjuvant chemoradiotherapy bleomycin:** The exact mechanism is unknown. It occurs most commonly on the nails, back, elbows, and small joints. It is tan to brown to black and due to an increase in epidermal melanin at sites of minor trauma or inflammation. Parallel linear streaks at the site of dermatographism are induced by excoriation; this is called flagellate pigmentation.⁴⁵
- **Topical use of 5-Aminolaevulinic acid (ALA) in the treatment of superficial nonmelanoma skin cancers (superficial basal cell carcinoma, actinic keratosis, Bowen diseases, etc.) with photodynamic therapy.**⁴⁶
- **Adriamycin:** Pigmented patches in the oral mucosa, especially the lateral side of the tongue.
- **Hydroxyurea and zidovudine:** Nail bed (longitudinal bands) and tongue pigmentation. Brown macules on the lips or oral mucosa.

Hairs, nails, and/or mucous membrane may also be involved, with some distinctive aspects, such as dyschromia of the glans penis, during tegafur treatment course. Tegafur is a chemotherapeutic fluorouracil prodrug used in the treatment of cancers. Dyschromia of the tongue and oral mucosa during use of fluorouracil, doxorubicin, cisplatin, and hydroxyurea (hydroxycarbamide). Dyschromia of hairs occurs during treatment course with cisplatin and methotrexate. Nails may be affected by many agents, including cisplatin, doxorubicin, idarubicin,⁴⁷ and fluorouracil.⁴⁸ Bleomycin, docetaxel, dacarbazine, and hydroxyurea can cause depigmentation of the nails with longitudinal or transverse pigmented bands or diffuse nail pigmentation, sometimes coexisting with leukonychia or even onycholysis in case of docetaxel.

Drug-induced pigmentation is typical for up to 5% of busulfan users. Busulfan caused pigmentation occurs on face, the axillar region, chest, abdomen, and oral mucosa.

Metals and heavy metals

Treatment with metal- and heavy metal- containing drugs can cause depigmentation.³⁶

- **Gold:** Blue-gray hyperpigmentation of sun-exposed skin (chrysiasis) in 5%–25% of all treated patients. The process is dose dependent. Gold may produce purplish gingival discoloration. In the case of high-dose therapy, pigmentation may occur in a short time; in contrast, in the case of low-dose therapy, it occurs after months. Pigmentation persists long after the drug is discontinued. Pigmentation is frequently more pronounced around the eyes. Its source is organic colloidal gold preparations used in therapy for rheumatoid arthritis; there have also been some dermatological indications, such as pemphigus vulgaris.
- **Silver:** Generalized slate-gray pigmentation on sun-exposed areas (face and dorsa of the hands), nails, sclera, and mucous membranes (argyria or argyrosis). The use of silver salts is currently restricted to rare cutaneous

uses, for example, silver sulfadiazine, and ocular topical uses. Its sources are silver nitrate nose drops and silver sulfadiazine as an ointment. There are several case reports of localized pigmentation occurring after long topical or environmental exposure to silver, for example, silver earrings⁴⁹ and acupuncture needles.^{50,51} Localized pigmentation after long exposure to silver salts have been reported as well but appear to be much less frequent than the generalized subset. The mechanism of action is silver sulfide (silver nitrate converted into silver sulfide by light, as in old-fashioned photographic film).

- **Iron:** A low level of hemoglobin and ferrum in the body is routinely treated with iron injections. Brown or blue-gray discoloration is caused, in some individuals, could be generalized. A very common finding is local deposits at the site of injection.

Many of the heavy metals have been formerly implicated in producing oral hyperpigmentation (such as lead, bismuth, and mercury). Indeed, mercury and bismuth are not used therapeutically now, although industrial or accidental exposure is still occasionally seen.⁵²

Heavy metal-induced hyperpigmentation is a frequent event. The indications of silver and, to a lesser extent, gold salts have been largely reduced over the last decades. The occurrence of this pigmentation is usually slow, insidious after years of treatment (probably triggered by a threshold cumulative dosage), and the etiological diagnosis is sometimes difficult to establish since patients often forget to mention topical medications that have been used for years. After discontinuation of the medication, a very slow improvement may be observed, but a residual pigmentation is often observed.

Localized pigmentation has been described as occurring under gold jewelry⁵³ and on an area exposed to Q-switched ruby laser treatment in a patient receiving long-term gold sodium thiomalate therapy for psoriatic arthritis.⁵⁴

Psychotropic drugs

Psychotropic drugs include phenothiazines (chlorpromazine), tricyclic antidepressants (imipramine and desipramine), and anticonvulsants.⁴ High doses and a long duration of use (year or more) of phenytoin cause spotty discoloration, resembling melasma, more often on light-exposed areas and due to melanin. Progressive slate or blue-gray pigmentation can be seen on sun-exposed areas.

In the case of chlorpromazine hyperpigmentation, it appears that the pigmentation generally reverses within months to years of discontinuing therapy. The use of other neuroleptics, including other phenothiazines, does not cause pigment disorders or lenticular changes to persist, whereas corneal changes may slowly resolve.^{55–57}

Slate-gray pigmentation has been noted with desipramine⁵⁸ and imipramine,⁵⁹ which are structurally related to chlorpromazine. Blue-grey pigmentation has been reported with stelazine,⁶⁰ desipramine,⁶¹ and imipramine,⁶² and clomipramine has been noted to cause a pseudocyanotic discoloration.⁶³

Anticonvulsants

Anticonvulsants, such as phenytoin, hydantoin, and barbiturates, may induce skin pigmentation with a pattern of melasma for hydantoins or a diffuse brown, postexanthematous discoloration for barbiturates.

ACTH

Oral hyperpigmentation may be seen in ACTH therapy, Addison's disease, Nelson's syndrome, or ectopic ACTH production (e.g., by bronchogenic carcinoma). An interesting fact about ACTH is that the chain of the first 13 amino acids is similar to α -MSH. Pigmentation caused by ACTH clinically remains Addisonian pigmentation.

Carotene

As a rule, it results in yellow-orange skin color, mostly on the palms and soles. The source is ingestion of large quantities of β -carotene-containing vegetables or β -carotene tablets.

Cyclophosphamide usually causes brown, diffuse macular pigmentation on the elbows and palms with Addisonian-like pigmentation.

Estrogens stimulate melanin production, and drug-induced hyperpigmentation may be seen with the combined oral contraceptive.

Hyperpigmentation has also been reported with oxprenolol,⁶⁴ and minocycline–amitriptyline combinations.⁶⁵

Clofazamine is widely used in the treatment of leprosy; it produces orange, reddish-brown discoloration. Typically ill-defined pigmentation on light-exposed areas; conjunctivae, and as discoloration of urine and faces.⁶⁶

Other medications with a possible relation to skin discoloration are chlorhexidine, griseofulvin, crack, and cocaine.

DIAGNOSTIC POINTS

- Medical examination with a full medical history regarding drug intake and its chronology.
- Careful skin examination of the skin and mucous membrane looking for the mentioned elements.
- Careful information about drugs taken and their potential ability to induce dyschromia.
- The relevance of the pigmentation and its chronology, occurrence, progression, and fading with respect to the intake of the noted or suspected drugs.
- Additional examination—histology, electron microscopy, mass spectrometry. Methods can display specific patterns of the presence of pigments, melanin accumulation, and free or included pigment in dermal macrophages.

Patch testing may give a positive result and help determine the triggering medication when several drugs are received at the same time; these tests are all the more interesting when they are performed at the site of the eruption.

A definite diagnosis often needs a protracted follow-up, which is not always carried out by the same physician.

Another well-known clinical pattern, very reminiscent of drug-induced pigmentation, is called the fixed drug eruption—circumscribed, well-delimited, sometimes geographically shaped pigmented macules following inflammatory lesions.

Unless other causes of hyperpigmentation, such as melanoma, hyperthyroidism, hemochromatosis, and Addison's disease, are considered, a dermatological consultation may be unnecessary, although skin histopathology may aid in the determination of potential etiologies. Treatment includes potential drug discontinuation or the use of topical agents to mask the pigment changes.

The differential diagnoses are as follows:

- Endocrine and metabolic disorder–related pigmentation
- Addison's disease
- Melasma and chloasma
- A wide range of different conditions accompanied by pigmentary disorders
- Vitamin deficiencies—mainly in nicotinic acid and vitamin B12 and photoaggravated pigmentation
- Riehl's melanosis

MORPHOLOGY

Histological findings are very variable as well, but the colored particles are often concentrated within dermal macrophages that are sometimes localized in a distinctive fashion with respect to dermal structures such as vessels or adnexes.

Histologic findings of drug-induced hyperpigmentation are quite variable and depend on the causative factor. Usually, melanin, another pigment, or both can be found either free in the dermis or within dermal macrophages.

Histological findings show deposits of amiodarone and lipofuscin in dermal histiocytes that contain dense bodies of osmiophilic material in the case of amiodarone-caused hyperpigmentation. Histology on minocycline hyperpigmented lesions shows accumulation of melanin, hemosiderin, lipofuscin, and minocycline itself.

Histology on pigmented areas in the case of antimalarial hyperpigmentation shows an increase in the quantity of melanin, but also of hemosiderin in the lower epidermis and dermis.

It must be emphasized that histological examination usually does not help to differentiate drug-induced pigmentation from other similar dyschromia in as much as both groups often display the same chromophore, melanin, in standard slides, except in heavy metal-dependent pigmentation.^{36,67}

Histologic examinations of pigmented lesions display silver granules smaller than 1 μ m in diameter scattered in sweat glands, around hair follicles and dermal vessels, and in the upper dermis with a predilection for elastic fibers. These granules are free or found inside fibroblast cytoplasm in lysosome-like bodies.⁶⁸

Histological diagnosis may be helped by the presence on paraffin wax-embedded sections of a peculiar orange-red birefringence of the pigment, not detected in other histologically similar deposits.⁶⁹

The cutaneous discoloration is most likely secondary to dermal granules containing melanin bound to the drugs or their metabolites in the case of chlorpromazine.⁷⁰

TREATMENT (TABLE 14.1)

Polymedication is usually encountered in elderly patients, which makes it all the more difficult to associate a

Table 14.1 Possible treatments.

1. The most important therapeutic intervention is the identification and discontinuation of the offending agent. After discontinuation of the medication, discoloration usually resolves spontaneously in months to years. Although cutaneous or mucosal pigmentation may appear regardless of the dose or duration of treatment, permanent discoloration generally results from cumulative doses.
2. Careful adjustment of the daily dosage according to body weight or any other applicable parameters.
3. As drug-induced hyperpigmentation is often worsened by sun exposure, sun avoidance is an essential part of treatment.
4. General recommendations: Those persons using risky medications need special considerations in preventing and treating various etiologies of drug-induced hyperpigmentation. Peak hours of sunlight (between 11:00 a.m. and 4:00 p.m.) should be avoided, in addition to seeking shade and wearing protective clothing (e.g., broad-brimmed hats and long-sleeved shirts). Avoiding provoking triggers is necessary for reducing risk of hyperpigmentation.
5. Several studies have shown that light from both the ultraviolet (UV) and visible spectrum can induce pigmentary changes in the skin.^{71,72}
6. Bleaching agents, such as hydroquinone, are not effective due to the dermal location of the pigment.
7. Topical treatment: 0.05% tretinoin cream at bedtime, 0.1% clindamycin lotion twice daily, and 10% benzoyl peroxide daily spot treatment.
8. Laser therapy has recently been reported to give promising results in some cases. Q-switched ruby (694 nm), alexandrite (755 nm), and Nd:YAG (1064 nm) lasers have all been used to lighten the blue-black hyperpigmentation caused by minocycline with good results.^{73–77}
9. Significant cosmetic improvement of hyperpigmentation induced by hydroxychloroquine or amiodarone has also been reported after treatment with the Q-switched ruby laser.⁷⁸
10. MIH acne scars may be excised surgically.
11. Resolution of MIH with fractionated photothermolysis.⁷⁹
12. Oral isotretinoin.⁸⁰

pigmentary change to a given drug, especially when the chronology of an insidious dyschromia is unclear.

In most cases, it is far easier to prevent drug-induced pigmentation from occurring than it is to treat it. Avoiding drug-induced pigmentation is not always easy or desirable when it requires the daily dosage of an essential medication to be lowered.

Treatment is often limited to sun avoidance or interruption of treatment with the offending drug, but laser therapy recently gave rise to hope of a cure in some cases. These measures are often followed by a fading of the lesions, but the pigmentation may last for a long time or may even become permanent in a small percentage of patients.

It is essential to obtain an understanding of the problem by patients in order to ensure compliance, and this requires the provision of a clear explanation of the risk by the physician who prescribes the drug, emphasizing the often observed lack of complete disappearance of the pigmentation even after discontinuation of the drug.

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BACKGROUND

Hyperpigmentations are congenital or acquired skin conditions linked to alterations in the melanin pigment. They can be classified as epidermal, dermal, or mixed form, in which coexist the epidermal and dermal patterns. They are related to an increase in the number of melanocytes or in the production of melanin. Pigmentary disorders are a frequent source of complaints, and they are reported to be the second most common complaint between 15 and 30 years of age, and the first in the range of 40–50 years, regardless of skin color and gender.¹ Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis occurring after cutaneous inflammation or injury that can be seen in all skin types, but more frequently affects patients with Fitzpatrick skin types IV through VI. This acquired excess of pigment can be attributed to various conditions that affect the skin, such as infections, allergic reactions, mechanical injuries, reactions to medications, phototoxic eruptions, and burns. PIH can also appear after treatments such as ultrasound, radio frequency, lasers, and other light therapies, as well as secondary to microdermabrasion. PIH is most severe in patients whose basal cell layer of the epidermis is disrupted, such as in conditions like lichen planus, lupus erythematosus, atopic dermatitis, and other lichenoid dermatoses. PIH has a significant psychosocial impact on patients, even though there are many safe and effective options to treat it, including topical depigmenting agents, chemical peels, and laser and light therapy. This chapter describes the epidemiology, etiology, pathogenesis, clinical features, diagnosis, and treatment options for PIH.^{2,3}

EPIDEMIOLOGY

PIH is an acquired condition in which excessive melanin deposition occurs at sites of skin inflammation or injury. It occurs more commonly in individuals with darker skin (Fitzpatrick skin types III–IV through VI). Examples include African Americans, Hispanics or Latinos, Asians, Pacific Islanders, and Middle Eastern people. PIH has no sexual or age predilection and can occur with equal incidence in males and females and in people of any age. Many epidemiological studies have shown that PIH tends to occur more commonly among black patients than Caucasian patients. A study confirmed dyschromias to be the second most common diagnosis among African American patients, but dyschromias failed to make it into the top 10 most common diagnoses for Caucasian patients.⁴ A study conducted in Singapore⁵ showed a higher prevalence of PIH among Asians with darker skin

(such as Malays and Indians) than those with lighter skin (such as the Chinese). This finding suggests that the degree of pigmentation, rather than race or ethnicity, may contribute more to the development of PIH. People with higher skin phototypes, presumably, are more inclined to this skin condition because they already have a higher basal amount of epidermal melanin. Similarly, PIH tends to be more intense and long in this group of people.⁶

ETIOLOGY

Many types of inflammatory dermatoses or cutaneous injuries can cause PIH, including infections (viral exanthemas or fungal infection), trauma, allergic reactions (insect bites or contact dermatitis), phototoxic eruptions, papulosquamous diseases (psoriasis or lichen planus), hypersensitivity after medication (tetracycline, bleomycin, doxorubicin, 5-fluorouracil, busulfan, arsenicals, silver, gold, antimalarial drugs, hormones, and clofazimine), cutaneous T-cell lymphoma (especially erythrodermic variants), burns, and cosmetic procedures (Table 15.1).^{7,8} Other common causes of PIH, especially in black patients, are acne vulgaris, atopic dermatitis, impetigo, and pseudofolliculitis barbae. Among African Americans with pseudofolliculitis barbae, the prevalence of PIH is estimated between 45% and 83%.^{9,10} When PIH affects people with acne, it can sometimes also be triggered by aesthetic interventions (dermabrasion, chemical peels, or laser therapies).

PATHOGENESIS

When an injury, rash, or any other kind of influence causes skin inflammation, this can trigger melanocytes to release excessive melanosomes. These melanosomes contain tyrosinase and synthesized melanin. PIH results from the overproduction of melanin or an irregular dispersion of pigment after cutaneous inflammation. Cutaneous pigmentation is regulated by a complex melanogenic network in which both keratinocytes and fibroblasts synthesize growth factors and cytokines; in fact, several chemical mediators appear to play a role in PIH.¹¹ In the epidermal PIH, the inflammatory response results in the release and subsequent oxidation of arachidonic acid metabolites, such as leukotrienes (e.g., LT-C₄ and LT-D₄), prostaglandins E₂ and D₂, thromboxane 2, interleukins (e.g., IL-1 and IL-6), tumor necrosis factor- α (TNF- α), epidermal growth factor, and reactive oxygen species (e.g., nitric oxide).¹² Other biologic effects on the cells may arise as a result of arachidonic acid itself, which, applied to the skin in small or large amounts, causes hyperplasia of keratinocytes, as well as marked proliferation of epidermal

Table 15.1 Etiology of PIH.

Infections	Viral exanthems
	Fungal infections
Allergic reactions	Insect bite
	Contact dermatitis
Cosmetic procedures	Depigmenting agents
	Chemical peels
	Laser and light therapy
Hypersensitivity after medications	Tetracycline
	Bleomycin
	Doxorubicin
	5-Fluorouracil
	Busulfan
	Arsenical
	Silver
	Gold
	Antimalarial drugs
	Hormones
	Clofazimine
Cutaneous T-cell lymphoma	
Trauma	
Burns	
Acne vulgaris	
Impetigo	
Infection by pseudofolliculitis barbae	
Phototoxic eruptions	

pigment cells and enhancement of melanization.¹³ Dermal PIH results from inflammation-induced damage to basal cell layer keratinocytes, which release large amounts of melanin (also known as pigmentary incontinence). The free pigment is then phagocytosed by macrophages and produces a blue-gray appearance to the skin at the site of injury. Furthermore, as highlighted in some studies, fibroblast-derived melanogenic growth factors may be crucial in mesenchymal-epithelial interactions modulating melanocyte function.^{14–16} In fact, the interactions between mesenchymal and epithelial cells lead to the release of keratinocyte growth factor (KGF) that, alone or in combination with IL-1 α , induces hyperpigmented lesions. Besides, a moderate increase of KGF and a high induction of its receptor have been shown in solar lentigo lesions, suggesting the involvement of KGF in the onset of the hyperpigmented lesions.¹⁷ Another study established that the increased expression of endothelin 1 and endothelin receptor, as well as the stem cell factor (SCF) and SCF receptor (c-KIT), is mainly responsible for the activation of melanocytes in the epidermal hyperpigmentation of ultraviolet B (UVB) melanosis and lentigo senilis. The same authors examined the paracrine cytokine mechanism involved in seborrheic keratosis epidermal hyperpigmentation, comparing the stimulatory effects of IL-1 α or TNF- α on SCF production between seborrheic keratosis cells and normal human keratinocytes. They showed that

seborrheic keratosis cells do not respond to IL-1 α or TNF- α to stimulate production of SCF, whereas a significant stimulation of SCF is elicited by those same cytokines in normal human keratinocytes.¹⁸ Another paper analyzed the involvement of the fibroblast-derived growth factors, KGF and SCF, in hyperpigmentation induced by UV exposure. The findings of the study showed that fibroblasts may be persistently activated, for example, by UV exposure, to release melanogenic growth factors, and that this inducible cytokine network acts both directly and indirectly through keratinocytes and may contribute to the development of hyperpigmentation. In fact, the authors demonstrated positive staining for KGF and SCF in the upper dermis of pigmented lesions, a significant induction of the cytokines in photoaged fibroblasts, and the possibility of KGF modulating the expression of SCF in keratinocytes.¹⁹

CLINICAL FEATURES

PIH appears as spots of discoloration. These macules can range in color from pink to red, brown, or black, depending on skin tone and depth of discoloration. PIH typically manifests as macules or patches in the same distribution as the initial inflammatory process. The distribution of spots follows the location of the inflammatory processes, and collecting this information from the patient is very important to establish the correct differential diagnoses. The location of the excess pigment within the layers of the skin will determine its coloration. Epidermal PIH appears tan, brown, or dark brown and needs months to years to resolve without treatment. Dermal PIH has a blue-gray appearance and may either be permanent or resolve after a long time if left untreated.^{20,21} The timing depends on the difference in skin tone between the natural skin tone and the darkened patches. The more significant the difference, the longer it will take for the tones to rebalance. The intensity of PIH may also correlate with higher skin phototypes. PIH does not cause scarring, and even with no treatment, it will improve over time. On average, it can take from 3 to 24 months for the darkened areas to fade, although in some cases it may take longer. In addition, PIH can worsen with UV irradiation or with persistent or recurrent inflammation. Histology shows melanin deposits both in free form and within the melanophages located in the upper dermis and around the blood vessels.

DIAGNOSIS

Diagnosis of PIH is usually made clinically. In a patient's medical history, a previous pathologic process, such as inflammation or trauma of the affected area, is present. Skin biopsy is performed to exclude other underlying causes of hyperpigmentation in cases when a prior event is questionable. Histological findings depend on the localization of the excess pigment; increased melanin pigment in the basal cell layer of the epidermis is present in epidermal PIH, while dermal PIH is characterized with melanin pigment in the upper dermis and increased numbers of melanophages in the papillary dermis, which lead to pigment incontinence.

Examination under Wood's lamp can also determine localization of the pigment with accentuated borders in epidermally located pigment or the discreet appearance of dermal lesions.

DIFFERENTIAL DIAGNOSES

When approaching this condition, it is very important to exclude other hyperpigmentations, the etiology of which is not postinflammatory (Table 15.2).

THERAPY

One of the very important factors for the successful management of PIH is prior treatment of underlying inflammatory dermatosis that caused PIH. A proper localization of the lesion and analysis of the patient's skin phototype are necessary in order to set a more appropriate treatment, which should lead to the disappearance of skin discoloration without leaving permanent scarring or discoloration. Adequate timing for starting with treatment is extremely important because although early treatment might halt disease progression and prevent further hyperpigmentation, it can also irritate the skin and aggravate PIH.²²

The importance of photoprotection should not be underestimated because it prevents disease progression. This has to be emphasized particularly to darker-skin individuals who, unfortunately, rarely use daily broad-spectrum sunscreen, as well as other sun-protective measures.²³

Treatment of PIH includes topical agents, surgical therapy, and cosmetic camouflage (Table 15.3).³ Therapeutic efficacy of topical agents is higher in cases of epidermal PIH, and for significant improvement, topical creams are often combined with chemical peels and sunscreens.²⁴

Hydroquinone (HQ) has remained the mainstay of treatment.³ Besides its inhibition effect on tyrosinase, it is also selectively toxic toward melanocytes and it inhibits melanocyte degradation.^{25,26} Its therapeutic concentrations are from 2% to 4%, but it can also vary up to 10% as an over-the-counter (OTC) drug in the United States. It has satisfactory therapeutic efficacy when used as a monotherapy, but the combination of HQ with other topical agents, such as retinoids, antioxidants, glycolic acid, sunscreens, and corticosteroids, increases its efficacy.⁸ The

Table 15.3 Treatment of PIH.

Topical agents	Hydroquinone
	Retinoids
	• Tretinoin
	• Adapalene
	• Tazarotene
	Azelaic acid
	Corticosteroids
	L-Ascorbic acid (vitamin C)
	Others
	• Kojic acid
	• Licorice extracts
	• Niacinamide
	• N-Acetylglucosamine
	• Soy
	• Mequinol
	• Arbutin
Surgical therapy	Chemical peels
	• Glycolic acid
	• Salicylic acid
	Laser treatments
	• Frequency-doubled QS Nd:YAG (532 nm)
	• QS ruby (694 nm)
	• QS alexandrite (760 nm)
	• QS Nd:YAG (1064 nm)
	Intense pulsed light (IPL)

Note: QS, Q-switched.

combination of HQ with retinoids can lead to skin irritation, but this can be minimized when using it with topical corticosteroids.²⁷ HQ-induced side effects include contact dermatitis, permanent leukoderma, nail discoloration, and hypopigmentation of the surrounding normal skin that has been treated with HQ ("halo effect").²⁵

Structural and functional analogues of vitamin A, retinoids, reduce hyperpigmentation with their different anti-inflammatory and biological effects: from modulation of cell proliferation, differentiation, and cohesiveness to induction of apoptosis.²⁸ Agents used in the treatment of PIH are tretinoin, a first-generation retinoid and naturally occurring metabolite of retinol, and synthetically derived third-generation retinoids, adapalene and tazarotene. Topical retinoids are available in different concentrations and formulations; concentrations of retinol range from 0.01% to 0.1%, and adapalene from 0.1% to 0.3%, while tazarotene is available in 0.05% and 0.1%. Third-generation retinoids have shown satisfying therapeutic results, especially in darker-skinned individuals with acne-induced PIH.^{29,30} Topical tretinoin can also be applied as a peeling mask—high tolerability and efficacy have been noted in melasma patients treated with a 10% tretinoin peeling mask.³¹

Retinoid-induced dermatitis is a common side effect of topical tretinoin therapy, so it is highly recommended to

Table 15.2 Differential diagnosis of PIH.

Acanthosis nigricans
Addison's disease
Ephelides
Erythema dyschromicum perstans
Fixed drug eruptions
Hemochromatosis
Lentigo
Lichen planus
Melasma
Systemic drug-induced pigmentation
Tinea versicolor

adjust timing, dose, and form of topical tretinoin before starting the treatment.²²

Azelaic acid is an isolate produced by yeast that lives on normal skin, *Malassezia furfur* (also known as *Pityrosporum ovale*). It reduces hyperpigmentation by inhibiting tyrosinase. Also, it inhibits DNA synthesis and mitochondrial enzymes, and therefore has cytotoxic and antiproliferative effects toward abnormal melanocytes.³² It is available in 15% and 20% concentrations, and it is mainly used for treating melasma and acne-induced PIH.^{33,34} Overall, 20% azelaic acid is nontoxic and very well tolerated.

L-Ascorbic acid (vitamin C) is a natural antioxidant that induces skin lightening by reducing oxidized dopa-quinone, a substrate in the melanin synthetic pathway, and also by interacting with copper ions at the tyrosinase active site.^{25,35} Available concentrations of ascorbic acid are between 5% and 10%, and literature reports are mainly related to the treatment of melasma.^{36,37} Usually, it can be combined with HQ with a good safety profile.³⁸

The rationale for using topical corticosteroids in PIH treatment is mostly in its anti-inflammatory effect. Usually, topical corticosteroids are used in combination with topical HQ and retinoids with satisfying therapeutic results.³⁹

Chemical peeling (chemexfoliation) represents the controlled skin damage with caustic agents. Controlled skin destruction involves the epidermis and/or dermis and results in regeneration of new epidermal and dermal tissue.⁴⁰ This procedure is usually done with glycolic acid, salicylic acid, and trichloroacetic acid. This type of procedure, due to its ability for penetrating into the papillary dermis and its good therapeutic response, is also recommended for patients with darker skin types.^{8,41} In most cases, superficial chemical peelings are well tolerated, regardless of skin phototype. Possible side effects can manifest as burning sensation, erythema, superficial desquamation, reactivation of herpes simplex virus (HSV), PIH, hypopigmentation, hypertrophic scarring, and keloid formation.⁴² In cases when photoprotection after treatment is not regularly applied, worsening of PIH can occur; therefore, it is very important to emphasize the role of sun protection to patients. Before starting the procedure, in order to avoid complications, a detailed patient history and complete skin examination should be performed, including prior reactions to other cosmetic procedures, history of HSV infection, and current medications.^{43,44} Glycolic acid is part of the alpha-hydroxy acid (AHA) family of natural ingredients, originally produced in sugarcane. Its mechanism of action is based on epidermolysis, dispersion of basal layer melanin, and an increase of dermal collagen synthesis.⁴¹ Concentrations of glycolic acid vary between 20% and 70% with good therapeutic response in dark-skin patients (Figure 15.1).⁴⁴ Salicylic acid is a beta-hydroxy acid that disrupts intercellular lipid linkages between epithelioid cells and induces keratolysis.^{8,41} Its therapeutic concentration ranges from 20% to 30%, and it has a good efficacy and safety profile in even higher skin phototypes,



Figure 15.1 PIH and scar in periorbital area 6 months after single treatment with 60% glycolic acid peeling.

V and VI.⁴⁵ Although trichloroacetic acid has mostly been used as a chemical agent for melasma treatment, literature evidence is still sparse for its usage in PIH.⁴⁶

Even if the therapeutic validity of the classical surgical ablative laser, such as CO₂ and erbium lasers, has been known for several years, the continuing technological advances have allowed the introduction of new devices that are more selective and efficient for the treatment of PIH: the Q-switched lasers (Table 15.3).^{47,48}

Q-switched lasers typically produce very short pulses (nanoseconds) with high peak powers (megawatts).

In each case, laser treatment of PIH is based on the theory of “selective photothermolysis,” and the target chromophore is represented by melanin, which is synthesized by melanocytes and contained in melanocytes and keratinocytes of the lesion. A selective window for targeting melanin lies between 630 and 1100 nm; the target’s absorption decreases as the wavelength increases, but a longer wavelength allows deeper skin penetration. Besides wavelength, the pigment specificity of lasers also depends on their capacity to produce very short pulses, which allow the destruction of a more selective target.⁴⁹

The therapeutic protocol depends on the characteristics of the lesion and the treatment. The most important side effects that have been reported are transient erythema, blistering, and discromias.⁵⁰

Recently, the combination of ablative and pigment selective lasers has also been tried for the treatment of melasma and other PIHs. While ablative lasers remove the epidermis (containing excess melanin and abnormal melanocytes), the successive use of Q-switched pigment-selective lasers reaches deeper lesions in the dermis (dermal melanophages) without causing serious side effects.⁵¹

Another emerging concept in the laser treatment of PIH is fractional photothermolysis, which is characterized by multiple microscopic zones of thermal damage, with sparing of the majority of the skin.⁵² The multiple columns of thermal damage lead to extrusion of microscopic

epidermal necrotic debris, which includes pigment in the basal layer. The advantages of fractional laser therapy are linked to avoiding an open wound, so that the recovery is faster and complications (such as discromias) are limited.

Finally, for the treatment of PIH there is the intense pulsed light (IPL). This procedure uses a pulsed source of light energy that is broad spectrum, not coherent or collimated.⁵³ While not exactly a laser, the IPL has the same indications of the major dermatological laser currently in use. The possibility of combining the IPL's parameters (wavelength, pulse duration, interval between pulses, and fluence) in various ways has increased the effectiveness of the technique in the treatment of pigmented lesions.

The variable pulsed light (VPL) is similar to IPL, but instead of one flash of light, energy is provided in a few small and rapid microflashes.

Avoidance of exposure to UV light should be emphasized to all patients prior to laser therapy. In order to obtain an optimal therapeutic response, broad-spectrum sunscreens should be applied at least 6 weeks prior to

any aesthetic procedure in general and particularly laser treatment.⁵⁴

Although monotherapy of PIH can yield a good therapeutic response, in some cases, a combination of topical creams and gels, chemical peels, and sunscreens may be necessary for significant improvement.⁵⁵ For patients with a darker skin phototype, chemical peeling with glycolic acid can be effective when combined with tretinoin and HQ.⁵⁶ A slightly more aggressive treatment, 0.1%–0.4% aqueous all-*trans* retinoic acid combined with HQ–lactic acid ointment, showed good therapeutic results in the Oriental population.⁵⁷ Treatment was further combined with topical corticosteroid, HQ, and ascorbic acid for promotion of the healing process. Literature reports about fixed combinations of 4% microencapsulated HQ and 0.15% retinol with antioxidants or sunscreen find that they are safe and effective for both PIH and melasma.^{58,59}

The famous Klingman's formula, originally containing 5% HQ, 0.1% tretinoin, and 0.1% dexamethasone in hydrophylic ointment, was a preferable therapeutic option for

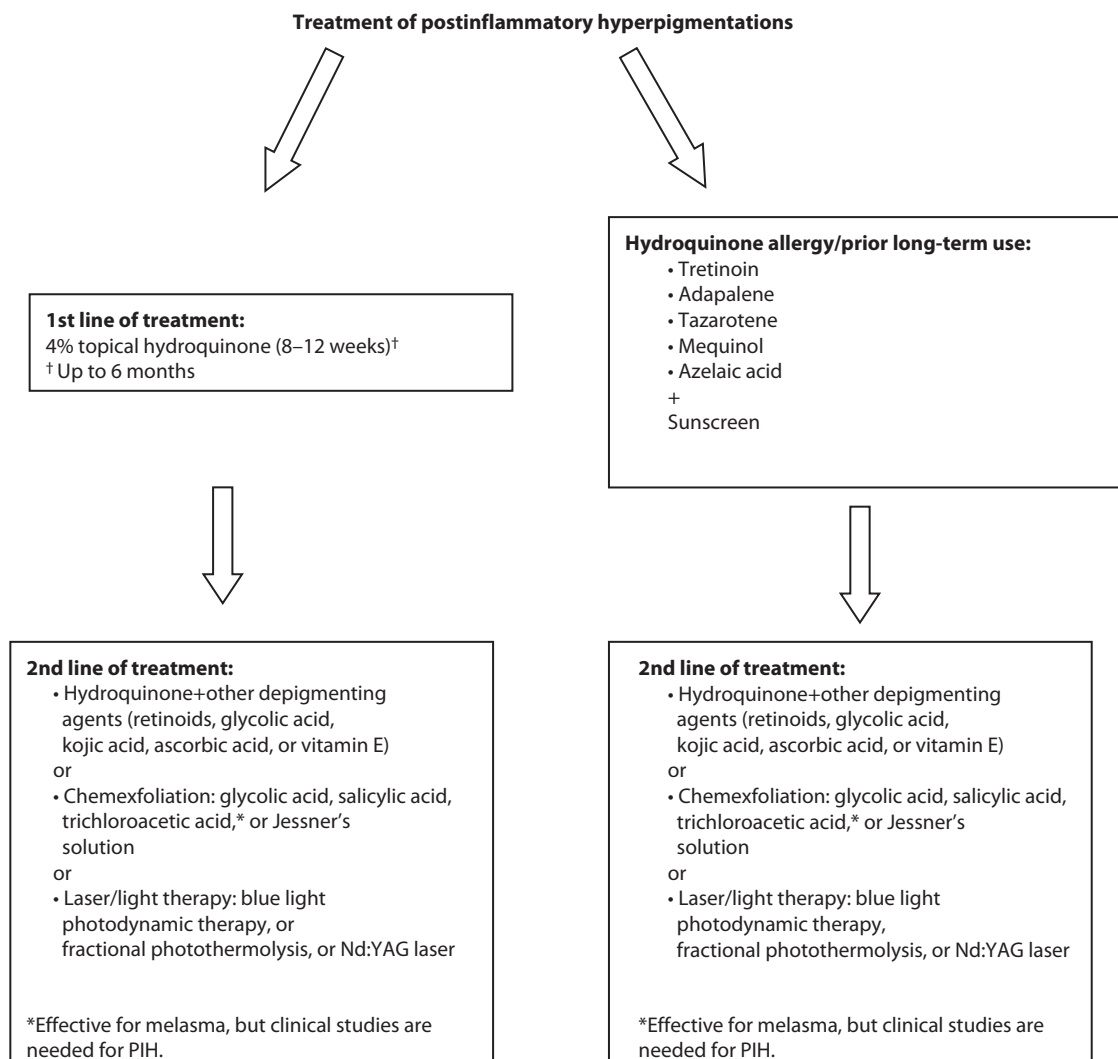


Figure 15.2 Management strategy for PIH. (Adapted from Davis, EC, and Callender, VD, *J Clin Aesthet Dermatol*, 3(7), 20–31, 2010.)

many decades in the treatment of hyperpigmentations.⁶⁰ Due to its use of high concentrations of tretinoin and a potent fluorinated steroid, it has been modified in many ways over the years to be made more adequate for different skin types. A combination of 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide appears to be safe and effective in the treatment of melasma, but more clinical studies are necessary to evaluate its therapeutic role in PIH.⁶¹

Anti-inflammatory and antioxidant properties of extracts of the tropical fern *Polypodium leucotomos* might be beneficial in the treatment of PIH. No controlled studies have assessed the efficacy of *P. leucotomos* for the treatment of PIH. Nevertheless, *P. leucotomos* significantly improved the severity of melasma, so it might also have an adjunctive role in the treatment of PIH.⁶²

Several years ago, Davis et al. suggested a therapeutic algorithm for the management of PIH—a useful indicator for directing physicians to safe and efficacious therapeutic options for PIH (Figure 15.2).³

CONCLUSION

Treatment of PIH can sometimes be very challenging. It might be considered the state of the art—appropriate timing for starting with treatment is crucial because it has to be early enough to prevent disease progression, but also should not irritate skin and cause worsening of the disease. Hopefully, treatment options are numerous, including the variety of topical depigmenting agents, chemical peels, and laser therapy.⁶³ Sun protection involving broad-spectrum sunscreen, as well as other sun-protective measures, is an important factor in the management of the disease and also in retaining successful therapeutic results.

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PIGMENTARY DEMARCATION LINES (FUTCHER'S LINE AND VOIGT'S LINE)

Definition

Pigmentary demarcation lines (PDLs) are lines that separate zones of light and dark skin color on different areas of the body. They are more obvious in some people than in others and are usually symmetrical, arising on both sides of the body.

Epidemiology

Skin pigmentation shows interesting variations in a single race or in an ethnic subpopulation. In a prevalence study in an outpatient clinic in India, 243/4037 (6%) of the patients were found to have demarcation lines on their face. The demarcation lines were far more common in women (9%) than in men (0.75%). About 25% of black Africans show sharply demarcated pigmentary lines at either the antero-lateral upper arm or the posteromedial part of the lower limbs.¹⁻⁴

Pathophysiology

PDLs occur in all races and skin types. The separation of zones corresponds to the lines of Blaschko, indicating that they are a common manifestation of cutaneous mosaicism. Hormonal influences could possibly explain the female preponderance. An aggregation of cases within families or among close relatives suggests a genetic background.

Clinical features

PDLs are physiological, abrupt transitions from darker-colored skin to lighter-colored skin. All PDLs first make their appearance around puberty and tend to persist throughout life. Different shades of skin color may first be noticed in infancy and persist into adulthood.

About 50% of the patients presented to the dermatology department with the complaint of pigmentation, whereas an additional 25% were aware of the problem but did not complain of it. The rest of the patients were unaware of the pigmentation.

The most common PDL is type PDL-A, which presents with darker skin on the outer aspect of the arm than on the medial aspect. The contrast between the two colors may be accentuated following sun exposure.

Classification and location

PDLs have been reported to occur in six areas of the body, each assigned a label:

- PDL-A, which occurs between the lateral and medial aspects of the upper arms, extending into the pectoral skin

- PDL-B, which occurs on the posteromedial portion of the lower limbs
- PDL-C, which occurs on the mediosternal line, with a vertical hypopigmented line in the pre- and parasternal areas
- PDL-D, which occurs on the posteromedial area of the spine
- PDL-E, which occurs as bilateral hypopigmented streaks or bands over the skin of the chest in between the midthird of the clavicle and the periareola skin
- PDL-F, which occurs on the face around the lateral cheeks and periorbital skin (Figure 16.1)

PDLs over the face have been categorized into different clinical patterns in the Indian subpopulation. They were classified into three patterns, as F, G, and H of PDLs.⁵

Of the total female patients surveyed, 4.56% presented with hyperpigmented patches that appeared V shaped or as an inverted cone on the lateral aspect of the face in the region between the malar prominence and the temple (PDL-F).

A total of 1.48% of the females had the pigmentary patch in the same location, but had two inverted cones lying in close proximity, looking like the letter W, with a faint strip of normal pigmentation in between (PDL-G).

In 2.2% of the study population, two symmetrical linear bands of hyperpigmentation extending from just below the angle of the mouth to the lateral aspects of the chin were observed (PDL-H).⁵

Extracutaneous signs

There are no extracutaneous signs.

Histopathology

The histopathology is usually unremarkable except for increased melanization in occasional cases.

Differential diagnoses

Melasma, postinflammatory pigmentation, café-au-lait macules, and Becker's nevi may occasionally mimic PDL.

Treatment

Patients with facial PDLs often seek treatment for cosmetic reasons. Unfortunately, there is no definitive and effective treatment at present. Sun avoidance and regular use of broad-spectrum sunscreen may minimize the color contrast of the lighter and darker skin areas. Topical bleaching agents and chemical peels have been tried with minimal effects.

LINEAR AND WHORLED NEVOID HYPERMELANOSIS

Definition

Linear and whorled nevoid hypermelanosis (LWNH) is a sporadic pigmentary disorder appearing within the first

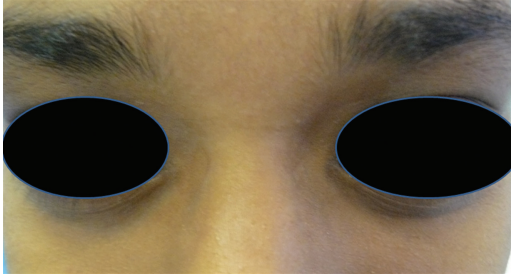


Figure 16.1 Dark PDL around the periorbital skin (PDL-F). (Courtesy of the National Skin Centre, Singapore.)

weeks of life with characteristic swirls and streaks of macular hyperpigmentation following the lines of Blaschko. The condition was first described in 1988 by Kalter and colleagues.⁶

Synonyms include zosteriform hyperpigmentation, zosteriform lentiginous nevus, zebra-like hyperpigmentation, reticulate hyperpigmentation of Iijima, and nevoid hyperpigmentation following Blaschko's lines.^{7,8}

Epidemiology

Both sexes are equally affected.⁹ The occurrence is usually sporadic, although familial cases have also been described.^{7,10}

Pathophysiology

The cause of LWNH is not known.⁶ Underlying chromosomal mosaicism has been demonstrated in a few reports. The exact pathogenesis is unknown. Genetic mosaicism, leading to the proliferation and migration of two populations of melanocytes with different potentials for pigment production, is the most likely cause of this disorder.¹¹

Clinical features

The common presentation is the diffuse form of LWNH. Some present with the unilateral form (progressive cribriform and zosteriform hyperpigmentation type). Sites of predilection include the trunk and extremities.

The linear streaks and swirls of macular hyperpigmentation occur in a reticulate pattern without any preceding inflammation, following the lines of Blaschko (Figure 16.2). LWNH displays a V-shaped pattern over the spine, an S-shaped or whorled pattern over the anterior and lateral aspects of the trunk, and a linear pattern on the extremity or genitalia.¹¹ The palms, soles, scalp, and mucous membranes are typically spared.¹²

The hyperpigmentation usually appears within a few weeks of birth.⁷ It tends to progress for 1–2 years before stabilization and usually persists indefinitely.

Extracutaneous signs

The hyperpigmentation often occurs alone, but additional symptoms have been reported to be associated in some individual cases.

LWNH may be associated with growth retardation, developmental delay, intellectual disability, seizures,



Figure 16.2 Swirls and streaks of macular hyperpigmentation following the lines of Blaschko on the trunk. (Courtesy of the National Skin Centre, Singapore.)

skeletal anomalies (e.g., scoliosis, pectus excavatum, brachydactyly, and body asymmetry), central nervous system anomalies (e.g., hydrocephalus, macrocephaly, microcephaly, and arhinencephaly), congenital heart diseases (e.g., ventricular septal defect), and chromosomal abnormalities (e.g., mosaic trisomies 7, 14, 18, and 20).

Histopathology

Histopathology examination shows diffuse increased pigmentation in the basal layer and a prominence of melanocytes without incontinence of pigment in the dermis.¹²

Differential diagnoses

The differential diagnoses include incontinentia pigmenti, hypomelanosis of Ito, and linear epidermal nevus (EN).

Incontinentia pigmenti almost always occurs in girls and is generally fatal in boys; associated defects are present in 80% of patients. The cutaneous manifestations of incontinentia pigmenti usually progress through four stages.¹³ The first stage presents with erythema, vesicles, and pustules; the second stage with verrucous lesions; the third stage with hyperpigmented streaks or whorls; and the fourth stage with hypopigmentation, atrophy, and scarring. The hyperpigmentation that characterizes the third stage is present in most patients and usually fades by adolescence.

In hypomelanosis of Ito, the skin lesion consists of seemingly bizarre macular, hypopigmented streaks, stripes, whorls, and patches that conform to the lines of Blaschko.¹⁴ The lesions always involve more than two body segments.

Linear EN presents as skin-colored or brown, closely set, well-circumscribed papules in a linear configuration. The lesion usually occurs on the trunk, neck, or an extremity and follows the lines of Blaschko. Linear EN tends to become hyperkeratotic, papillomatous, verrucous, and hyperpigmented with time.

Treatment

There is no effective treatment for this condition. For lesions in cosmetically sensitive areas such as the face, skin camouflage creams are a useful option.

LINEAR MORPHEA OR EN COUP DE SABRE

Definition

Morphea is relatively uncommon disorder that affects adults and children. It is characterized by excessive collagen deposition, leading to thickening of the dermis, subcutaneous tissues, or both, often associated with epidermal atrophy.

Epidemiology

The incidence of morphea is estimated to be approximately 0.4–2.7 per 100,000 people in the United States. Females are affected approximately three times as often as males.

Pathophysiology

Morphea is associated with an overproduction of collagen (especially types I and III) by dermal fibroblasts and an increase in the extracellular matrix in the dermis. Other pathogenic mechanisms proposed include the presence of antidermal metalloproteinase antibodies and an increased expression of insulin-like growth factor, which enhances collagen production.^{15–17}

Clinical features

Morphea is classified into several different types according to the appearance of the skin lesions, viz., superficial (circumscribed or plaque morphea) and deep variant.

Superficial variant (the most common) presents with discrete, circumscribed, indurated plaques measuring 1–20 cm or more in diameter, mainly on the trunk, with a violaceous border and indurated center. Over time, sclerosis develops centrally and the surface becomes smooth, shiny, and ivory in color, with loss of hair follicles and sweat glands. The lesion eventually involutes over time.

The deep variant involves the subcutaneous fat and underlying structures, such as muscle and fascia, presenting with ill-defined, bound-down, sclerotic plaques with a “cobblestone” or “pseudocellulite” appearance. The lesions are frequently hyperpigmented. Linear morphea (en coup de sabre) is one of the presentations (Figure 16.3). Morphea typically has a benign, self-limited



Figure 16.3 A hyperpigmented, indurated, and atrophic linear plaque located on the left paramedian area of the forehead. (Courtesy of the National Skin Centre, Singapore.)

course. Survival rates for morphea patients are no different from those of the general population. However, linear and deep morphea subtypes can cause considerable morbidity.

Extracutaneous signs

Joint contractures, limb length discrepancy, and prominent facial atrophy result in substantial disability and deformity in a quarter to half of all patients with linear or deep morphea.

Histopathology

The epidermis is usually normal with flattened rete ridges. In the early inflammatory stage, a perivascular and interstitial infiltrate of lymphocytes, plasma cells, and occasional eosinophils is seen. Blood vessel walls demonstrate endothelial swelling and edema, and thickening of preexisting collagen bundles. In the late sclerotic stage, the inflammatory infiltrate typically disappears. Collagen bundles in the reticular dermis and subcutis become thick, closely packed, and hyalinized. Adnexal structures appear to be trapped within the middle of the thickened dermis as subcutaneous fat is replaced by collagen.

Differential diagnoses

Differential diagnoses include lichen sclerosus, eosinophilic fasciitis, lichen striatus (LS), and linear lichen planus (LLP).

Treatment

Lesions of superficial circumscribed morphea often undergo gradual spontaneous resolution over a 3- to 5-year period. Limited disease can often be managed with topical therapy (steroids, immunomodulators, and calcipotriene) or phototherapy. Imiquimod cream (5%) three to five times per week has been shown to decrease lesional erythema and induration in small series.

Successful treatment of severe and/or rapidly progressive morphea with systemic corticosteroids in combination with weekly low-dose methotrexate (MTX) has been reported in several case series. Mycophenolate mofetil is a second-line agent. Phototherapy may be beneficial as a second-line therapy.

Linear morphea is generally more recalcitrant to treatment and often leaves behind contractures and permanent scars. Treatment includes intralesional steroid injections. Physiotherapy is often recommended to prevent joint contractures when morphea affects the limbs.

ACQUIRED BLASCHKOID DERMATITIS

Definition

Acquired Blaschkoid dermatitis (BL) is a rare skin condition of unknown cause. It was first described in 1990 by Grosshans and Marot.¹⁸ It is also known as blaschkitis, or idiopathic dermatitis along the lines of Blaschko. It is believed to represent the adult form of LS.

Epidemiology

BL occurs equally in both sex and all ages.

Pathophysiology

Controversy exists regarding the pathogenesis and classification of BL. It is sometimes considered to be a variant of childhood LS. BL and LS have similar histological epidermal changes and inflammatory dermal infiltrates consisting of a lichenoid lymphocytic infiltrate with exocytosis of inflammatory cells and obvious alterations of the interface zone. Some authors proposed to unify similar diseases with similar clinical and histopathological features with common genetic pathomechanisms, but with phenotypic variations, as BL has been reported in young children as well.²⁰

Clinical features

BL never presents at birth and is very uncommon in children. It presents as acquired inflammatory skin lesions looking like dermatitis or eczema. The affected skin appears red, inflamed, and irritated (Figure 16.4). Patients often complain of relapsing inflammatory linear lesions consisting of pruritic, papulovesicular eruptions along Blaschko's lines on the chest or back or limbs. Multiple bands along the lines of Blaschko may be present. It is usually unilateral, affecting one side of the body.

BL is diagnosed clinically by its characteristic appearance. Sometimes a skin biopsy is necessary to differentiate it from other skin conditions that may arise in Blaschko's lines.

Extracutaneous signs

There are no extracutaneous signs.



Figure 16.4 Linear erythematous scaly plaques following the line of Blaschko on the right preauricular region extending to right jawline.

Histopathology

Histopathological examination often shows spongiotic dermatitis and rarely necrotic keratinocytes and exocytosis of lymphocytes in the stratum spinosum.

Differential diagnoses

Differential diagnoses include contact and endogenous dermatitis, Köbner's phenomenon from various dermatoses, epidermal nevi, linear porokeratosis, LLP, and linear lichen nitidus.

Treatment

BL lesions may resolve spontaneously, but they have a tendency to relapse over time, especially associated with stress. Mild localized acquired BL does not require treatment. Dryness may be managed with topical emollient and avoidance of skin irritants, including avoidance of soaps. Generally, topical steroids are ineffective. A few case reports have reported that systemic steroid therapy was effective.

LINEAR EPIDERMAL NEVUS

Definition

EN is an overgrowth of the epidermis arising from a defect in the ectoderm. It often presents at birth (50%) or develops during childhood (usually in the first year of life). Types of epidermal nevi include linear EN, epidermolytic EN, acantholytic EN, linear porokeratosis, systematized EN, and inflammatory linear verrucous EN (ILVEN).²¹

Epidemiology

EN affects approximately 1 in 1000 people.

Pathophysiology

EN arises because of the proliferation of one abnormal population of skin cells, resulting in a localized area of thickened skin. EN is distributed along the lines of Blaschko. Skin cells that have the abnormal gene spread out to form the EN. A point mutation in keratin genes is involved in the development of epidermal nevi. Mutations in the FGFR3 gene have been found in approximately 30% of people with a type of nevus in the keratinocytic EN group. The gene mutations involved in most epidermal nevi are unknown. Mutations associated with an EN are present only in the cells of the nevus, not in the normal skin cells surrounding it. Because the mutation is found in some of the body's cells, but not in others, people with an EN are said to be mosaic for the mutation. Keratin 1 and keratin 10 gene abnormalities have been found in parents who have an epidermolytic EN and in their offspring who have a bullous ichthyosiform erythroderma.²²

Parents of a child with an EN should generally not be at increased risk for other affected children, because the mutation did not arise within their sperm or eggs, but within the fetal tissue. However, there is some risk that the individual with an EN could pass the mutant gene onto his

or her offspring, if his or her germline tissue is also mosaic for the mutation.²³

Clinical features

EN is a clinical term for a family of skin lesions that involve the epidermis and are distributed in a linear and often swirled pattern. The lesions may be single or multiple and are usually present at birth. All epidermal nevi show some changes in texture, which can range from very rough, warty, and spiny, and often darker than the surrounding normal or uninvolved skin (verrucous EN) (Figure 16.5), to red and scaly (ILVEN), to yellowish, rough, and pebbly due to proliferation of oil- or sebaceous gland-like structures (nevus sebaceous). If they involve the epidermal linings of the hair follicles, they are known as nevus comedonicus.

Epidermal nevi usually arise on the trunk and limbs, and are less common on the face or scalp. The majority are linear epidermal nevi; i.e., they form a line, usually unilaterally on one side of the body. When they first appear at birth or in infancy, they are flat brown marks but as the child ages, they become thickened and often warty. The nevus may also become more extensive over the years. Another name for a linear EN is nevus unis lateralis.

Epidermal nevus syndromes²³

The EN syndromes refer to the association of an EN with abnormalities in other organs derived from the embryonic ectoderm. These syndromes may involve the eyes, bones, or nervous system. Many specific syndromes have been described. Named syndromes include

- CHILD syndrome
- Proteus syndrome
- EN with bone cysts and hypophosphatemic rickets
- Nevus comedonicus syndrome
- Sebaceous nevus syndrome
- Phakomatosis pigmentokeratotic
- Becker's nevus syndrome



Figure 16.5 Dark brown verrucous papules coalescing into linear plaques on the right neck. (Courtesy of the National Skin Centre, Singapore.)

Complications of epidermal nevi

Most epidermal nevi remain unchanged in adulthood and do not cause any problems. However, very rarely another tumor can arise within the lesion. This may be a harmless syringocystadenoma papilliferum, or rarely a malignancy, including keratoacanthoma, basal cell carcinoma, or squamous cell carcinoma. A skin biopsy may be necessary if there is any suspicious change in the appearance of the nevus.

Extracutaneous signs

Systematized epidermal nevi are less common. They present with multiple lesions that usually arise in a swirled pattern, on one or both sides of the body. In some patients, there are also other congenital abnormalities, particularly of the skeleton and central nervous system (EN syndrome).

Histopathology

Histologically, the EN shows increased thickness of the epidermis. The rare epidermolytic EN variety is characterized by epidermolytic hyperkeratosis resembling features seen in bullous ichthyosiform erythroderma. The acantholytic EN variety has features resembling Darier disease. Linear porokeratosis has features resembling disseminated superficial actinic porokeratosis.

Differential diagnoses

Differential diagnoses include epidermodysplasia verruciformis, erythrokeratoderma variabilis et progressiva, keratosis follicularis (Darier disease), lichen planus (LP), LS, and porokeratosis.

Treatment

There is no real effective medical treatment for epidermal nevi. Topical calcipotriol may reduce the verrucosity in some cases. If necessary, laser or surgical removal of nevi may be performed under local anesthesia. But there is a tendency for such epidermal nevi to recur over time.

BECKER'S NEVUS

Definition

Becker's nevus (BN) was first documented in 1948 by American dermatologist Samuel William Becker (1894–1964).^{24,25} It is also known as Becker's melanosis, Becker's pigmentary hamartoma, nevoid melanosis, and pigmented hairy EN. It is a late-onset EN occurring more commonly in males than females. It is a relatively common skin disorder. It presents with a mild to moderately hyperpigmented skin patch with velvety texture and coarse vellus hairs. It typically occurs on the trunk during childhood or adolescence and occasionally in a patchy pattern rather than a linear pattern.

Epidemiology

It is more common in men. One study reported a prevalence of 0.52% in men aged 17–26 years.²⁶

Pathophysiology

The nevus is due to an overgrowth of the epidermis, melanocytes, and hair follicles.²⁷ The pathogenesis of BN remains unclear. While it is generally considered an acquired disorder, there exists at least one case report of a congenital BN with genetic association: a 16-month-old boy with a hyperpigmented lesion on his right shoulder whose father has a similar lesion on his right shoulder.²⁸

It is thought that it is due to a gene defect, which has not yet been identified. It may be triggered to develop by circulating androgens, which is why it tends to make its appearance in males at puberty.

Clinical features

BN is a late-onset EN occurring mostly in males. The nevus usually presents as a large, one-sided, irregular, brown, pigmented patch over half the upper back or chest or shoulder or upper arm (although other areas of the body can be affected) (Figure 16.6). It gradually enlarges irregularly, becoming thickened and often a hairy patch. It often expands and becomes darker and quite hairy over 1–2 years after puberty. Occasionally, acne may develop in the nevus. One case of bilateral, symmetrical pigmentation is reported—this is unusual.²⁹

The apparently most extensive study to date, a 1981 survey of nearly 20,000 young Frenchmen, served to disprove many commonly held beliefs about the disorder.²⁶ In the French study, 100 subjects were found to have Becker's nevi, revealing a prevalence of 0.52%. Nevi appeared in one-half the subjects before the age of 10, and between ages 10 and 20 in the rest. In one-quarter of cases, sun exposure seems to have played a role, a number apparently lower than that expected by researchers. Also surprising to researchers was the low incidence (32%) of Becker's nevi above the nipples, for it had generally been believed that the upper chest and shoulder area was the predominant site of occurrence. Pigmentation was light brown in 75%



Figure 16.6 Hyperpigmented brown patch on the left chest associated with hypertrichosis. (Courtesy of the National Skin Centre, Singapore.)

of cases (note that the subjects were Caucasian), and the average size of the nevus was 125 cm² (19 in.²).

Generally, the nevus color will fade, but incompletely during adulthood. The nevus persists indefinitely.

Malignancy

A 1991 report documented the cases of nine patients with both BN and malignant melanoma.³⁰ Of the nine melanomas, five were in the same body area as the BN, with only one occurring within the nevus itself. As this was apparently the first documented co-occurrence of the two diseases, there is so far no evidence of higher malignancy rates in Becker's nevi. Nonetheless, the nevus should be monitored regularly and a biopsy done should there be sudden changes in appearance.

Extracutaneous signs

A variant called BN syndrome^{30–32} presents with breast and/or skeletal hypoplasia or abnormality in the underlying tissues derived from the same embryonic cell type (the ectoderm) in the same region as the nevus. This is known as the BN syndrome, an EN syndrome. These abnormalities may include smooth muscle hamartoma (overgrowth of smooth muscle tissue); underdevelopment of underlying structures, such as the breast, pectoral muscle, fat, limb, chest wall, or spine; and overdevelopment of a tissue, such as the adrenal gland, limb, fingers or toes, or scrotum.

Histopathology^{29,30}

The epidermis of Becker's nevi shows acanthosis and hyperpigmentation of the basal layer, with elongation and fusion of adjacent rete ridges and variable hyperkeratosis. The dermis shows hyperplasia of the dermal smooth muscle and melanophages.

Differential diagnoses

Differential diagnoses include Café-au-lait macules, McCune–Albright syndrome (with café-au-lait patches on the skin) and postinflammatory hyperpigmentation (PIH).

Treatment

There is no effective treatment for the majority of Becker's nevi.³³ However, the nevus dark brown color becomes less obvious if the affected area is kept out of the sun so that it does not tan.

As BN is considered a benign lesion, treatment is generally not necessary except for cosmetic purposes. Shaving or trimming can be effective in removing unwanted hair, while electrolysis or laser hair removal may offer a longer-lasting solution. The results of laser treatments for both hair and pigment reduction appear to be highly variable. PIH is a common complication from laser therapy (Q-switched pigment and fractional lasers have been tried), especially in patients with darker skin types. Recurrences of the pigmentation occur almost consistently following pigment laser treatment.

BN-associated acne can be treated with standard acne therapies.

LINEAR LICHEN PLANUS

Definition

LLP, also referred to as Blaschkoid LP, is a rare type of LP characterized by a linear distribution of pigmented lichenoid lesions along the lines of Blaschko (embryonic pathways of skin development). It is inflammatory skin characterized by an itchy, noninfectious rash of small, polygonal, flat-topped, pink or purple papules on the arms and legs. Other parts of the body may also be affected, including the mouth, nails, scalp, vulva, vagina, and penis. Involvement in the scalp can result in hair loss—sometimes permanent. LP in ethnic skin tends to produce pigmented lesions, most likely as a result of postinflammatory pigmentation.

Epidemiology

According to the National Institutes of Health (NIH), United States, LP affects between 1% and 2% of the American population. According to the National Health Service (NHS), United Kingdom, around 1 in 50 people are affected by LP.

The prevalence is unknown. It has been reported to occur in 0.1%–4% of the general population, most often in perimenopausal women. LP can appear at any age, but most cases occur between 30 and 60 years of age.^{34,35}

Less than 0.5% of patients with LP present with Blaschkoid LP.

Pathophysiology

The etiology of LLP is unknown. An immune-mediated pathogenesis is proposed.³⁶ It has been associated with HIV infection, hepatitis C infection, and metastatic cancer.^{37–39} It is thought that LLP arises due to an abnormal keratinocyte clone that is only unmasked after the initiating event for LP. LP can also be triggered by taking certain medications, including thiazide diuretics, antimalarials, and phenothiazines (a group of tranquilizing drugs with antipsychotic actions). Noneczematous contact allergy can manifest with LLP. Three Japanese patients presenting with LLP on the lower extremities, unaccompanied by mucous lesion, were reported. Dental metal compounds were thought to be the precipitating factor in all cases. Two cases showed a positive patch test reaction to gold (HAuCl_4) and a positive lymphocyte stimulation test to gold compound (gold sodium thiomalate). One case showed a positive patch test reaction to mercury (HgCl_2), but a negative lymphocyte stimulation test. Suspected metal compounds were demonstrated in their dental materials. Removal of gold materials in one case gradually improved the lesions within 6 months, with a transient erythematous swelling of the face shortly after removal of the metal. These results suggest that metal compound-specific T cells might be responsible for the development of LLP.⁴⁰

Clinical features

LLP lesions appear as pruritic, violaceous papules in a linear distribution, usually on the limbs, but can occur anywhere on the body (Figure 16.7). LLP follows a Blaschkoid, nondermatomal pattern of distribution. It can be superimposed on the more typical nonsegmental and randomly distributed lesions of classic LP. A case of localized linear lichen planopilaris on the face, extending to the scalp, has been observed.⁴¹

LP can be diagnosed clinically in classic cases. Common LP lesions often appear in a linear configuration, following the lines of trauma (Koebner phenomenon). It is common to see PIH as the cutaneous lesions clear, especially in persons with darker skin.

A very rare LLP variant, called zosteriform LP, has also been observed and is characterized by a segmental zosteriform distribution of lichenoid lesions.⁴² Zosteriform LP may appear as a Koebner phenomenon following herpes zoster infection.

Extracutaneous signs

LP has been associated with HIV infection, hepatitis C infection, and metastatic cancer.^{37–39}

Histopathology

The histology is that of classical papulosquamous LP. A biopsy is often helpful to confirm the diagnosis. The classical histology shows a characteristic “sawtooth” pattern of epidermal hyperplasia, parakeratosis with thickening of the granular cell layer, and vacuolar alteration of the basal layer of the epidermis, with an intense infiltration (mainly T cells) at



Figure 16.7 Violaceous and brownish plaques in a linear distribution along the left jawline. (Courtesy of the National Skin Centre, Singapore.)

the dermal–epidermal junction and a lichenoid band of lymphocytic infiltrate in the upper dermis hugging the dermal–epidermal junction. Colloid bodies may be seen in direct immunofluorescence studies.

Differential diagnoses

Differential diagnoses include eczema, lichen simplex chronicus, prurigo nodularis, pityriasis rosea, psoriasis, and graft versus host disease.

Treatment

LP is not a curable condition. However, when it affects the skin it usually clears within 2 years. Treatment focuses on easing symptoms until the rash clears.

Mild cases require no treatment, except for periodic observations.

Treatment for more severe cases may include antihistamines, phototherapy, topical medications (e.g., topical steroids and immunomodulators), immunosuppressants, and systemic therapy, including oral steroids and immunosuppressants.

LINEA NIGRA

Definition

Linea nigra (LN) is a hyperpigmented vertical line that runs from the umbilicus to the pubic symphysis. Although commonly associated with pregnancy (when it is known as linea gravidarum), it has been found in normal males and females.

Epidemiology

The incidence of LN varies in different age groups, genders, and certain clinical statuses, such as pregnancy in women and benign prostate hyperplasia (BPH) or prostate carcinoma (PC) in men.

From a study assessing the incidence of LN in 1550 Nigerians, LN is more common in females and in the age group 16–30 years (47.3%) in clinically normal individuals. It is more often observed in pregnant women than in nonpregnant women of the same age.⁴³

LN was found to be more common in men with PC (48%) and BPH (26%) than in healthy controls (8%).⁴⁴

Pathophysiology

Considering the findings of an increased incidence of LN in teenagers, young adults, pregnant women, and men with BPH and PC, it would appear that hormonal influences are related to LN.^{43,44}

Hormonal changes associated with puberty would most likely explain the peak incidence of LN in the teenage years. However, not all teenagers have LN, suggesting that there may be other factors leading to a variable response of cutaneous melanocytes in the midline of the abdomen, such as genetic factors, a lack of sensitivity of androgen receptors, and some other physiological factors.⁴³

During pregnancy, there is a widespread increase in pigmentation, resulting in LN, darkening of the areola, nevi, and melasma. These physiological alterations in the skin have been attributed to the effect of estrogen levels, progesterone, and melanocyte-stimulating hormone (MSH).^{43,45–47}

It has been postulated that the presence of LN in men with BPH or PC may be due to some modification of the prostatic epithelium, which may be associated with the loss of androgen receptor immunoreactivity in the surrounding stroma.⁴⁸

Clinical features

LN presents as a dark brown linear line that runs from the umbilicus to the pubic symphysis (Figure 16.8). During pregnancy, it usually grows darker as the pregnancy progresses.^{43,45–47}

Extracutaneous signs

There are no extracutaneous signs.

Histopathology

No described histopathology of LN has been found in the literature.

Differential diagnoses

Differential diagnoses include PDLs and linear PIH.

Treatment

There is no treatment.

LN usually fades away shortly after the delivery of the baby and when the hormone levels stabilize in normal individuals.^{43,44}



Figure 16.8 Dark vertical line across the midabdominal skin associated with striae gravidarum. (Photo courtesy of Dr. Karen Choo, Department of Dermatology, Singapore General Hospital, Singapore.)

LINEA FUSCA

Definition

Linea fusca (LF) is characterized by a brown hyperpigmented band across the forehead, sparing the hairline. It is also known as brown forehead ring.^{49,50}

Epidemiology

LF usually affects adults. It has a distinctive pattern but is rarely reported.

Pathophysiology

The pathophysiology of LF remains unknown.

It was thought to be associated with neurological diseases such as epilepsy, neurosyphilis, Parkinson's disease, and cerebral tumors, but recent reported cases have no such association.^{49,50}

Photosensitivity, phototoxicity, and chronic actinic damage seem to play a role in some cases of LF.^{49,50}

Clinical features

LF usually presents as a brown or hyperpigmented band extending horizontally across the forehead, sparing the hairline.

Extracutaneous signs

Severe migraine or headache and epilepsy may be present in some cases of LF associated with neurological disorders.⁴⁹

Histopathology

An increase in pigment granules in the epidermal basal layer associated with limited pigmentary incontinence with no basal vacuolar alteration and mild lymphocytic infiltrate in the dermis has been shown.⁴⁹

Differential diagnoses

Riehl's melanosis, pigmented contact dermatitis, phototoxic and photosensitive reaction, and melasma are among the differential diagnoses.

Treatment

The treatment of LF is often challenging.

Treatments that have been tried include topical corticosteroid, Kligman's depigmentation cream, and topical azelaic acid.^{50–52}

Cosmetic camouflage should be used in recalcitrant cases.

If LF is thought to be associated with a neurological disorder, patients should be referred for neurological assessment and investigations.

LICHEN STRIATUS

Definition

LS is an uncommon dermatosis with a striking linear distribution primarily seen in children.

Epidemiology

LS mainly affects children between the ages of 4 months and 15 years and is more common in girls.^{53–55} Although rare in adults, LS may appear at any age.⁵⁵

Pathophysiology

The pathogenesis of LS remains unknown. It has been speculated that it could be due to loss of immune tolerance induced by an acquired stimulus, resulting in a cytotoxic reaction toward mutated, postzygotic skin cells distributed along Blaschko's lines.¹⁹

Environmental agents, cutaneous injury, viral infection, and a genetic predisposition that could trigger localized T-cell-mediated inflammation have been proposed as causative factors of LS.^{19,53}

Previous studies have found that LS occurs at a higher frequency in children with a personal or family history of atopy.^{55,56} Patients with atopy may have aberrant immune reactions that predispose them to the onset of LS, but it has not been established whether there is a causal relationship.^{55–57}

Kennedy et al.⁵⁸ observed the seasonal variation with an increased incidence of LS in the spring and summer, suggesting a possible viral trigger. Several reports have shown that viral infection (after an influenza-like fever, tonsillitis, varicella infection, or hepatitis B infection) or vaccination (Bacillus Calmette–Guérin, or measles, mumps, and rubella) may induce the development of LS.^{59,60} This has been postulated to be due to viral-induced loss of tolerance to the embryonic mutant clones distributed along localized Blaschko's lines.⁵⁶

Clinical features

LS is characterized by the presence of erythematous, lichenoid papules, ranging from 2 to 4 mm in diameter, that cluster in a continuous or interrupted linear pattern, sometimes reaching 1–3 cm wide along the lines of Blaschko (Figure 16.9). Hypopigmented macules and/or papules may



Figure 16.9 Linear lichenoid papules along the lines of Blaschko extending from the right thigh to THE right calf. (Courtesy of the National Skin Centre, Singapore.)

occur in dark-skinned people.^{56,61,62} LS is typically unilateral, occurring more frequently on the legs, although any part of the body may be affected.^{55,58}

LS usually presents with a sudden onset that progresses in days or weeks. It is typically asymptomatic, but intense pruritus can occur.^{53–56} Nail involvement is rare in LS, but onychodystrophy may occur and may appear before, after, or concurrently with skin lesions.^{58,62,63}

Extracutaneous signs

There are no extracutaneous signs.

Histopathology

Histopathological findings of LS include hyperkeratosis with occasional focal parakeratosis, mild spongiosis with exocytosis of lymphocytes, necrotic keratinocytes in the epidermis, and focal or lichenoid lymphocytic infiltrate in the papillary dermis. Superficial perivascular lymphohistiocytic infiltration may also occur, and there may be involvement of hair follicles and/or eccrine glands.^{53,56}

Differential diagnoses

Blaschkeitis, EN, ILVEN, LLP, linear psoriasis, and linear lichen nitidus are among the differential diagnoses.

Treatment

There is no effective treatment for LS. It is benign and self-limiting and may spontaneously resolve within 6–12 months without scar formation. Residual hyperpigmentation or hypopigmentation may persist for a couple of years.^{54,55}

Emollients may be used to treat dryness or pruritus, if present. Topical steroids or calcineurin inhibitors do not speed the involution of lesions but can be used to reduce pruritus.^{54,55} The combination of topical steroid and topical retinoid has been reported to speed up the resolution of LS.⁵⁴

LINEAR POSTINFLAMMATORY HYPERPIGMENTATION

Definition

PIH is a reactive hypermelanosis of the skin that occurs as a consequence of an inflammatory process, which can originate from endogenous or exogenous sources.^{64,65} Endogenous conditions may include acne vulgaris, atopic dermatitis, psoriasis, and LP, whereas exogenous conditions may include chemical peels, laser procedures, or contact with phototoxic agents.^{64–66} PIH typically presents as macules or patches that may be symmetrical, asymmetrical, diffuse, or in a linear pattern. The linear pattern of PIH is usually observed following contact with certain plants or fruits, most commonly lime, leading to phytophotodermatitis, or following cutaneous infections, such as herpes zoster and cutaneous larva migrans, or following excoriations leaving marks on the skin as a result of severe pruritus from insect bites, flare of atopic dermatitis, or neurotic excoriations.^{67,68}

Epidemiology

PIH can occur in any ages, both genders, and all skin types. However, it is more common in darker-skin patients with Fitzpatrick skin types IV–VI.^{64,66,69}

Pathophysiology

PIH results from either excess melanin production or an abnormal distribution of melanin pigment in the epidermis and/or dermis following cutaneous inflammation.^{64,65}

Although the exact mechanism is unclear, it has been shown that the melanocytes may have been stimulated by the increased amount of arachidonic acid metabolites, cytokines, inflammatory mediators, histamine, and reactive oxygen species that are released during the inflammatory process.^{64,65,70}

In epidermal PIH, there is an increase in the production and transfer of melanin to surrounding keratinocytes. In dermal PIH, inflammation causes damage to basal keratinocytes, resulting in the release of melanin in the dermis. This free pigment is then phagocytosed by macrophages (melanophages) in the upper dermis.^{64,65}

Clinical features

Linear PIH typically appears as asymptomatic linear brown patches or streaks, depending on the distribution of the original inflammation dermatosis. The linear pigmentation may appear in a dermatomal distribution if it occurs after herpes zoster infection (Figure 16.10).⁷¹ It usually affects the photoexposed part of the body and presents as bizarre streaks if it occurs after phytophotodermatitis (Figure 16.11).⁷² In cases of postcutaneous larva migrans, disorganized series of loops and tortuous tracks of pigmentation may form, most commonly on the feet, in the spaces between the toes, and on the hands, knees, and buttocks (Figure 16.12).⁶⁷ The linear PIHs from excoriations are usually similar in size and shape, and are grouped on easily accessible and exposed body sites, such as extensor surfaces of the extremities, face, and upper back (Figure 16.13).⁶⁸

PIHs appear tan, brown, or dark brown in color if the excess pigment is within the epidermis and darker gray or



Figure 16.10 Linear pigmentation appearing in a dermatomal distribution after herpes zoster infection. (Courtesy of the National Skin Centre, Singapore.)



Figure 16.11 Linear pigmentation on the fingers following phytophotodermatitis contact with lime juice. (Courtesy of the National Skin Centre, Singapore.)



Figure 16.12 Linear and tortuous tracks of hyperpigmentation following cutaneous larva migrans. (Courtesy of the National Skin Centre, Singapore.)

blue-gray if the excess pigment is within the dermis. The pigmentation can worsen with ultraviolet (UV) irradiation or with persistent or recurrent inflammation.^{65,73}

Extracutaneous signs

Postherpetic neuralgia may occur following the recovery of herpes zoster.⁷¹

Patients with neurotic excoriations often have a comorbid mental illness (usually anxiety, depression, or obsessive-compulsive disorder).⁶⁸

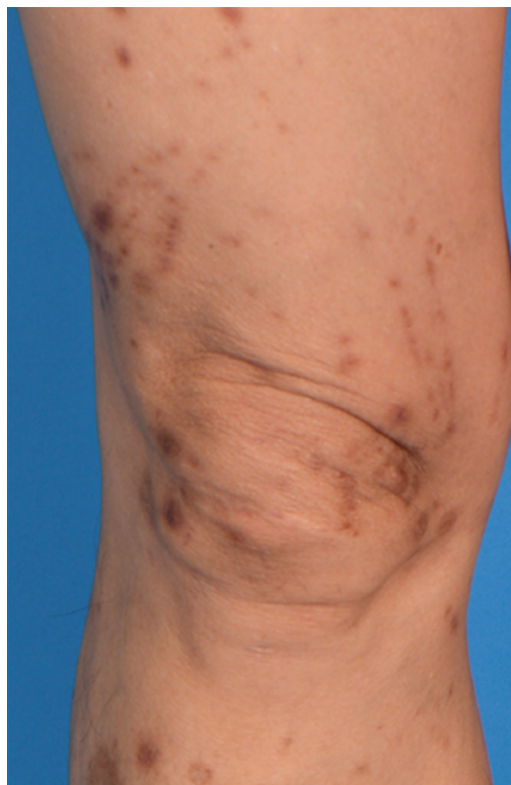


Figure 16.13 Linear hyperpigmentation on the right thigh as a result of excoriations. (Courtesy of the National Skin Centre, Singapore.)

Histopathology

The diagnosis of PIH is usually clinical if there is a history of a previous inflammatory condition. Skin biopsy is often unnecessary, but it can help to confirm the location of hypermelanosis. Histopathology will show patchy epidermal hypermelanosis and/or dermal melanosis and melanophages.⁶⁴

Differential diagnoses

Differential diagnoses include Stage 3 hyperpigmented incontinentia pigmenti, linear hyperpigmentation following chemotherapy, shiitake mushroom dermatitis, and dermatomyositis.

Treatment

The main treatment of linear PIH is the prevention and treatment of the underlying inflammatory condition. In general, an epidermal PIH clears faster than dermal PIH.^{65,74} An epidermal PIH may take months to years to resolve, and a dermal PIH may either be permanent or resolve over a protracted period of time if left untreated.^{64,65,74}

A variety of topical treatments are available to lighten epidermal PIH with varying degrees of success. These include topical bleaching agents, such as hydroquinone, azelaic acid, kojic acid, licorice extracts, arbutin, niacinamide, soy, retinoids, and vitamin C. Physical treatments, such as chemical peels, laser treatments, and intense

pulsed light (IPL) therapies, may be helpful, but may they also aggravate pigmentation.^{64–66,75}

These treatments are not effective in dermal hypermelanosis. Patients should use broad-spectrum sunscreens daily to reduce further darkening when outdoors. Cosmetic camouflage can also be used.^{64,65}

LINEAR HYPERPIGMENTATION FOLLOWING CHEMOTHERAPY

Pigmentary changes secondary to chemotherapy are common, but linear hyperpigmentation following chemotherapy is uncommon and may be underreported. It may present as serpentine supravenuous hyperpigmentation (SSH) following intravenous cytotoxic drug administration, such as 5-fluorouracil (5-FU), or as flagellate pigmentation, which is a unique side effect of bleomycin therapy.^{76–78}

Epidemiology

The exact epidemiology of linear hyperpigmentation following chemotherapy is not clear, as most incidents are reported as case studies.

SSH is most commonly associated with 5-FU.^{76,79} Other chemotherapy drugs, including alkylating agents, antibiotics, antimicrotubules, and proteasome inhibitors, such as fotemustine, vinorelbine, triazinate, and docetaxel, have been reported.^{79,80}

SSH occurs predominantly in men who are receiving treatment for solid tumors.⁷⁹

Flagellate pigmentation is a very characteristic finding associated with bleomycin therapy and is seen in about 20%–30% of cases.^{78,81,82}

Pathophysiology

The exact pathogenesis of SSH and flagellate pigmentation from bleomycin is not clear.

The possible hypotheses for SSH include loss of endothelial integrity caused by these cytotoxic drugs, resulting in leakage of these drugs to the epidermis. This may cause subclinical thrombophlebitis-induced PIH of the overlying skin. Some drugs, such as fotemustine, may cause direct melanocyte stimulation, and busulfan may promote melanin synthesis via removal of inhibitors of tyrosinase.^{76,80–84}

As for flagellate pigmentation, some authors suggested a traumatic mechanism from rubbing or scratching due to intense pruritus, resulting in increased leakage of the drug from dilated vessels, causing fixed drug eruption.⁸² The increased pigmentation is thought to be due to increased melanocyte stimulation by MSH, inflammatory oncotaxis, and adrenocorticotrophic hormone.⁸⁴

Clinical features

SSH presents as asymptomatic linear hyperpigmentation along the skin's overlying veins (Figure 16.14). It usually develops after several infusions of cytotoxic drug administration, such as 5-FU, fotemustine, vinorelbine, and triazinate.^{76,80}



Figure 16.14 Linear hyperpigmentation along the skin overlying veins that develop after several infusions of cytotoxic drug. (Courtesy of the National Skin Centre, Singapore. Photo courtesy of Dr. Hong Yi Koh, Department of Dermatology, Singapore General Hospital, Singapore.)

Flagellate pigmentation from bleomycin is generally pruritic and commonly affects the upper trunk and limbs.^{78,81} It is dose dependent, occurring after a cumulative dose of 15–285 mg given parenterally.^{83,85} The interval between the start of the treatment and the appearance of the flagellate pigmentation varies from a few hours up to 9 weeks and may persist for up to 6 months.^{81,83,85}

Extracutaneous signs

All chemotherapeutic drugs may induce mucocutaneous side effects, such as ulcers, stomatitis, glossitis, nail changes, and alopecia.^{82,85}

Histopathology

Histopathologic findings of SSH showed the presence of basal hyperpigmentation and pigment incontinence with no inflammatory changes.⁸⁶

The histopathology of flagellate pigmentation has been reported to show hyperkeratosis, focal parakeratosis, irregular acanthosis, and spongiosis within the epidermis. A band of basal hyperpigmentation and sometimes basal layer degeneration has been shown with lymphohistiocytic inflammatory infiltrate and melanophages in the dermis. Sometimes lymphocytic vasculitis without epidermis alteration can be seen.^{85,87}

Differential diagnoses

Shiitake mushroom dermatitis, dermatomyositis, and linear PIH are among the differential diagnoses.

Treatment

Linear hyperpigmentation from chemotherapy is generally benign and self-limiting. The pigmented streaks gradually resolve spontaneously after cessation of the medication.^{82,84,85}

As for SSH, central venous access routes could potentially be used to protect the skin overlying the peripheral veins from darkening.⁸⁴

PIGMENTARY LINES OF THE NEWBORN

Definition

Pigmentary lines of the newborn (PLN) is a rare, transient, benign hyperpigmentation in the newborn. It is also known as linear hyperpigmentation of the newborn.⁸⁸

Epidemiology

PLN is rare or may be underreported in the literature. Hence, there is little information about this condition.

Most reported cases involved black male newborns. It is uncommon in Caucasian newborns. There are only a few cases of PLN with a positive family history.⁸⁸

Pathophysiology

The cause of PLN is still unclear. It may be a consequence of friction or impaired exfoliation of the embryonic skin accentuated by the flexed position of the fetus *in utero* and other mechanical causes, resulting in postinflammatory pigmentation.^{89,90} It may also be due to mechanical trauma that induced hyperkeratosis within the skinfolds.^{89–91}

Clinical features

These horizontal lines appear at birth or a few weeks or months later and may involve the abdomen, extremities, and back.

PLN is characterized by the appearance of several horizontal lines or bands of hyperpigmentation that follow the skinfolds of the abdomen, back, or limbs at birth (Figure 16.15). These lines or bands subsequently fade spontaneously and resolve fully by 2–8 months of age.^{88–90}

PLN can be associated with abnormal cornification (ichthyosis vulgaris and collodion baby).^{90,92}

Extracutaneous signs

There are no associated extracutaneous anomalies.^{88,89}

Histopathology

No described histopathology feature of PLN has been found in the literature.



Figure 16.15 Horizontal pigmentary lines along the creases of the abdomen. (Photo courtesy of Prof. Peter Itin, Department of Dermatology, University Hospital Basel, Basel, Switzerland.)

Differential diagnoses

Differential diagnoses include hyperpigmentation secondary to congenital adrenal hyperplasia, pigmentary demarcation lines, and linear PIH.

Treatment

No treatment is necessary, as PLN fades spontaneously within 2–8 months.^{88–90}

HEEL-LINE OR SOCK-LINE HYPERPIGMENTATION

Definition

Heel-line or sock-line hyperpigmentation is also known as mitten-line hyperpigmentation. It is asymptomatic and presents as curvilinear, palpable, or nonpalpable bands on the extremities that may represent a reactive process to elastic bands in socks or mittens.⁹³

Epidemiology

Sock- or mitten-line hyperpigmentation usually appears in infancy and early childhood.⁹³ It has been described in Caucasian, Asian, and African American infants.^{94–96}

Pathophysiology

The exact pathogenesis is not clearly understood. It has been postulated that the circumferential hyperpigmented bands that resemble the tight sock-line bands or mittens may be due to prolonged trauma or compression from tight socks or mittens, leading to dermal inflammation or panniculitis, and hence resulting in PIH.^{93,94,97}

Furthermore, the age of onset of these lesions in infancy may be due to the presence of a higher percentage of saturated fatty acids in infantile fat, making it more vulnerable to adipocyte damage.⁹³

Clinical features

It typically presents as hyperpigmented horizontal curvilinear patches or plaques angled superiorly along the affected extremity at the sites of contact of elastic bands from socks or mittens. These bands may be partially or fully circumferential, single or multiple, unilateral or bilateral, and palpable or nonpalpable.^{93,94,97} In partially circumferential bands, the lesions typically appear over the posterior calves as opposed to the shins, most likely due to a higher proportion of subcutaneous fat in the calf or from greater pressure of the elastic band in this area.^{93,94}

Parents may report the presence of erythema at the sites before the development of the hyperpigmentation and may have attributed the multiple lines on the same calf to be from wearing socks of varying heights.⁹³

Extracutaneous signs

No extracutaneous signs have been reported.

Histopathology

Biopsy of these lesions has demonstrated lentiginous melanocytic hyperplasia and basal layer hyperpigmentation.^{96,98,99} This was thought to represent PIH, and there

was no comment on the presence of panniculitis in these biopsies.^{93,96,98}

Differential diagnoses

Child abuse, amniotic band syndrome, acquired raised bands of infancy (may be associated with limb defects, constrictions, club foot, and shortened toes), and incontinentia pigmenti are among the differential diagnoses.

Treatment

Sock- or mitten-line hyperpigmentation typically resolves within a few months, although persistence after 2–5 years has been reported.^{93,94,97,99}

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Flagellate hyperpigmentation

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INTRODUCTION

Flagellate dermatitis (FD) was described by Moulin et al. in 1971. The term comes from the Latin *flagellum*, derived from flagellant penitents in the Middle Ages, due to the linear lesions that resemble those produced by the act of whipping.¹⁻⁴ Typical lesions of FD are also described as striae and “zebra stripes.”⁵

Initially described as a bleomycin adverse effect, FD, also called flagellate erythema,⁶ is associated with the ingestion of raw or undercooked mushrooms, dermatomyositis, Still’s disease, and some drugs, such as bleomycin, among other causes.^{3,7,8}

The characteristic clinical presentation shows tracks or erythematous lines, parallel or irregular, usually pruritic, formed by numerous papules and vesicles, which can develop hyperpigmentation.^{2,5,7} Pigmented lesions distributed over pressure areas, as small joints of the hands, elbows, knees, and areas with striae, may also occur.⁵ However, there are some subtle differences in clinical presentation according to the etiology.⁷

Differential diagnoses of FD include contact dermatitis, herpes zoster, digitate dermatosis, and drug eruptions.⁹

BLEOMYCIN-INDUCED FLAGELLATE DERMATITIS

Bleomycin, a cytostatic antitumor drug derived from *Streptomyces verticillus*, is one of the chemotherapeutic agents that most commonly presents hyperpigmentation as an adverse effect.^{8,10} About 50% of all patients treated have skin reactions caused by the medication, administered either intramuscularly, intravenously, or intralesionally.¹¹⁻¹⁴ Besides FD, Raynaud’s phenomenon, scleroderma-like rash, mucosal lesions, nodular lesions, and pigmented nail bands may happen.^{11,15} The incidence of FD ranges from 8% to 20% in all patients treated with bleomycin.¹⁶

Bleomycin acts through the formation of oxygen free radicals that cause breaks in cell DNA and inhibit thymidine incorporation to DNA, resulting in cell death.^{14,17} The main uses of bleomycin are in the treatment of Hodgkin’s lymphoma, germ cell tumors, Kaposi’s sarcoma, squamous tumors of the head and neck, and gynecological tumors, and as a sclerosing agent in pleurodeses.^{14,17,18} Bleomycin is excreted by the kidneys and 60%–70% of the administered drug is eliminated in active form.¹⁴ The toxicity is mainly cutaneous and pulmonar, sites where drug levels are higher, since these organs lack bleomycin hydrolase, the enzyme responsible for the drug metabolism and its inactivation.^{1,5,19} Patients with renal insufficiency have greater difficulty in drug excretion, with an increased risk of toxicity.⁴

FD is characterized by red-purplish bands on the trunk and upper limbs that, in most cases, evolve to brown hyperpigmentation.^{5,7} Occasional blisters may occur, as well as mucosal and pulmonar lesions.^{4,20} Some patients describe itching immediately after bleomycin administration.⁷ Side effects may happen in different time frames, ranging from hours to days and even months after bleomycin administration.^{3,21,22}

Opposite to what was initially proposed, FD may occur even with low bleomycin doses.^{1,12,18,19,23} After withdrawal of the drug, the rash resolves, but residual hyperpigmentation can persist for up to 12 months.^{4,5} If bleomycin reexposure happens, lesions recur after a few hours and can arise in new areas.⁵ Lesion recurrence following heat exposure is described as “heat recall.”¹¹

The etiopathogenesis of FD is not completely understood, but it is believed that microtraumas, such as those generated by scratching, result in extravascular medication leakage, causing higher local bleomycin concentrations.^{2,7} The hyperpigmentation observed following the erythematous phase is possibly due to a reduction in the epidermal proliferation rate, which results in longer contact between keratinocytes and hyperfunctioning melanocytes.^{24,25}

Histopathological evaluation of acute bleomycin-induced FD shows findings similar to those found in the acute phase of fixed drug eruption: dyskeratotic keratinocytes, vacuolar basal layer degeneration, dermal infiltrate of lymphocytes and eosinophils, and incontinentia pigmenti.^{24,25} Lymphocytic vasculitis and increased epidermal melanin pigmentation may be observed.²⁵

The initial management of FD includes withdrawal of the drug and use of symptomatic medication for itch relief.²¹ After drug suspension, the dermatitis follows a self-limited course with resolution in weeks to months, yet residual hyperchromia may be persistent.^{16,26}

FLAGELLATE DERMATITIS ASSOCIATED WITH DERMATOMYOSITIS

Dermatomyositis, an autoimmune disease that affects predominantly skin and muscles, may be associated with FD, besides the classic symptoms.⁷ Small repetitive traumas and sun exposure possibly act as FD triggers.⁷ Idiopathic dermatomyositis is the most common form associated with FD.²⁷ However, some reports describe an association in amyopathic and also in paraneoplastic dermatomyositis.^{27,28}

Erythematous plaques and tracks, reflecting intense inflammation, characterize this form of FD. It follows dermatomyositis activity and usually regresses with treatment, but it usually lasts longer than the FD triggered by bleomycin.^{7,27,29}

Although uncommon, FD can be the first symptom of dermatomyositis and should be considered among the classical symptoms of the disease.²⁸

SHIITAKE DERMATITIS (TOXICODERMA): FLAGELLATE DERMATITIS TRIGGERED BY SHIITAKE MUSHROOM INGESTION

Shiitake mushroom (*Lentinus edodes*) is an Asian cuisine ingredient, the consumption of which is expanding.⁷ It is the second most consumed mushroom in the world, and 90% of the production is Chinese.³⁰ In addition, since shiitake mushrooms exhibit anti-hypertensive, immunomodulatory, and antitumoral properties, they are used in Oriental medicine, particularly as a chemotherapeutic agent.^{31,32}

Allergic contact dermatitis, shiitake dermatitis (SD) (toxicoderma), or FD induced by shiitake intake—and contact urticarial—are skin presentations that can be triggered by mushrooms.^{7,33} The inhalation of spores is responsible for allergic alveolitis.²⁴ Allergic alveolitis and shiitake contact dermatitis occur more commonly in people who grow and sell mushrooms.^{24,33,34}

SD develops in predisposed patients, generally 24–72 hours after eating raw or undercooked mushrooms. It is characterized by multiple, small, itchy, erythematous papules that arise and present a linear conformation

(Figure 17.1).^{7,10,31,35,36} The Koebner phenomenon is possibly involved in lesions' linearity.^{7,37} Petechiae may also be observed.^{37,38} The trunk is the most commonly affected region, followed by the extremities, neck, face, and head.³⁷ The mucous membranes, gastrointestinal tract, and nervous system are spared.^{20,37} Nonspecific changes in white blood cell count and transient elevation of liver enzymes are described in the literature.³⁷ Histopathologically, SD is characterized by spongiosis, elongation of epidermal ridges, and dermal edema with infiltration of lymphocytes and eosinophils.²⁴

An appropriate medical history, including eating habits, days before the appearance of lesions is of utmost importance for the diagnostic hypothesis formulation.^{9,20,31,39} Many patients present recurrence with subsequent mushroom intake. This fact allows rechallenge tests in doubtful cases.^{35,40} The patch test and prick test are not suitable and have negative results, because the process is not allergic.^{20,33,41} Corazza et al. observed a positive patch test in a patient with toxicoderma and questioned the assumption that this would be a toxic reaction. Even though an allergic delayed type IV reaction could be responsible for some cases, such cases are a minority in literature and require further investigation.³⁹ In addition, Kopp et al. described a case with a negative patch test and a positive prick test to raw shiitake, indicating an allergic delayed type IV reaction.⁴²

The main differential diagnoses of FD include chemotherapy reactions and connective tissue diseases, which can also evolve with the manifestations of FD.^{8,41}

The labile polysaccharide lentinan is believed to be involved in the pathogenesis of SD, through a toxic reaction.^{7,10,20,36,40,43} Although lentinan action is not completely understood, it possibly stimulates the secretion of interleukin 1 (IL-1), resulting in vasodilation, hemorrhage, and skin rash.⁴¹ After cooking at a temperature between 130°C and 145°C, lentinan undergoes helical conformation changes and is inactivated.⁴⁴ Reports describe toxicoderma as a consequence of consuming cooked mushrooms, but there is no assurance that these mushrooms were properly cooked to the point of allowing lentinan inactivation.⁴⁵

Drugs and genetic predisposition are also described in the pathogenesis of SD.³⁵ Furthermore, the possibility that lentinan might act as a photosensitizer is speculated.^{7,43,46} Hanada and Hashimoto reported 47% photosensitivity in 94 cases of SD in Japanese patients.⁴⁶

Tan and Tan consider that the way shiitake is grown can be associated with a higher incidence of toxicoderma. Since there are reports of SD after consumption of correctly cooked mushrooms, the theory that lentinan is the only related substance was brought into doubt. According to the author, shiitake cultivation on wood logs is associated with an increased risk of toxicoderma.⁴⁷

Garg and Cockayne describe a case of intermittent SD that lasted for 16 years until the correct diagnosis was made and the patient received proper orientation. In the reported case, a provocation test with the ingestion of undercooked mushrooms confirmed the diagnosis.⁴⁰



Figure 17.1 FD triggered by shiitake mushroom intake.

The eruption usually regressed spontaneously within 2 weeks of onset.^{31,37,43} SD is benign and self-limited, and resolves without persistent hyperpigmentation.⁴⁸

OTHER ETIOLOGIES

There is a report describing the occurrence of FD associated with parvovirus B19 infection in a pediatric patient that evolved to spontaneous resolution.²⁹

Other authors describe the association between FD and acral nodular dermatitis in one HIV patient receiving bleomycin treatment for Kaposi's sarcoma,² and a case of FD associated with the use of bendamustine chemotherapy in a patient being treated for chronic lymphocytic leukemia, reaffirming that FD may occur with other antineoplastic agents besides bleomycin.⁴⁹

TREATMENT

There is no specific treatment for FD.⁵⁰ Symptomatic therapy with topical, and sometimes systemic, corticosteroids, besides itch control with antihistamine administration to avoid skin traumas, may be helpful.^{21,45,51}

The recommendation to avoid eating raw mushrooms, preferring the properly cooked version, can prevent triggering SD in predisposed patients.^{20,37,38}

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INTRODUCTION

Reticular hyperpigmentation is a clinical feature that has been associated with a wide spectrum of disorders, including both congenital and acquired diseases. True macular reticular hyperpigmentation is quite rare and can be described as hyperpigmented macules or ephelide-like lesions that are arranged in a netlike pattern. This type of hyperpigmentation is encountered in disorders such as Dowling–Degos disease (DDD), acropigmentation of Kitamura, and incontinentia pigmenti (IP). However, reticular hyperpigmentation is also a feature of diseases such as reticulated papillomatosis of Gougerot and Carteaud, where the lesions are typically more elevated (papular) in nature. Finally, reticular hyperpigmentation can be observed in a number of acquired disorders as well. These include erythema ab igne, drug-induced reticulate pigmentation, and ashy dermatosis, among others.^{1,2}

The pathomechanism behind the appearance of reticular hyperpigmentation is not clear. This is mainly due to the fact that this clinical characteristic is associated with a wide variety of diseases that vary greatly in clinical manifestations, prognosis, and etiology. A summary of all diseases that can present with reticular hyperpigmentation can be seen in Table 18.1.^{1–13} In general, the disorders that may present with reticular hyperpigmentation can be classified as genetic or acquired. Proper diagnosis of each disorder can be achieved when the age of appearance, the distribution of lesions, and the presence, or type, of accompanying symptoms are taken into consideration (Table 18.1).

HISTOPATHOLOGY

Histopathological examination may also assist in setting the correct diagnosis. Overall, the disorders with reticulate hyperpigmentation can present with a variety of histopathological features, which can be crudely subclassified in four large categories. These include disorders with basal hyperpigmentation as a main characteristic, disorders with epidermal changes, disorders with striking melanin incontinence, and disorders with melanin incontinence and epidermal atrophy or “dyskeratotic” cells.¹⁴

Reticulate acropigmentation of Dohi (dyschromatosis symmetrica hereditaria [DSH]) commonly exhibits basal hyperpigmentation. More specifically, in patients with DSH basal areas of hyperpigmentation may alternate with areas of hypopigmentation. The number of melanocytes may also be decreased.¹⁵

Disorders such as acropigmentation of Kitamura, DDD, Galli–Galli disease (GGD), and confluent and reticulate papillomatosis of Gougerot and Carteaud (CARP) typically present with epidermal changes seen in the histopathological examination. More specifically, both DDD and GGD

exhibit acantholytic changes (more prominent in GGD). In addition, DDD may, in some instances, exhibit suprabasal lacunae, a feature more typical for GGD. These similarities are considered by some authors to indicate that GGD is a variant of DDD instead of a distinct entity.³ In DDD, basal hyperpigmentation is also present, but it is more prominent on the tips of the rete ridges. In hypopigmented areas, the hyperpigmentation is limited on the tips of the rete ridges and is completely absent from the basal layer.^{3,14} In acropigmentation of Kitamura, epidermal atrophy, hyperpigmented elongated rete ridges, and an increased number of melanocytes in the basal epidermis are usually observed.³ The epidermal changes observed commonly in patients presenting with CARP include acanthosis, hyperkeratosis, and papillomatosis. Basal hyperpigmentation may also be present.¹⁶

Naegeli–Franceschetti–Jadassohn syndrome (NFJS) and IP can exhibit striking melanin incontinence. This histopathological feature may also be present in acquired reticulate hyperpigmentation disorders, such as postinflammatory hyperpigmentation or prurigo pigmentosa.³ In NFJS, melanin is increased in the basal layers of the epidermis, while melanin incontinence is usually marked.^{14,17} In cases of IP, the histopathologic features vary depending on the stage of the disease. For instance, eosinophilic spongiosis with intraepidermal vesicle formation is considered typical for the first stage of the disease. In the second stage, where the verrucous lesion arises, acanthosis, hyperkeratosis, and mild irregular papillomatosis are usually present, while in the third stage of the disease, marked melanin incontinence is considered to be the most prominent feature.¹⁸

Finally, disorders that present with mixed features of melanin incontinence and epidermal atrophy or “dyskeratotic” cells include dyskeratosis congenital (DKC), “ripple neck” in atopic dermatitis, X-linked reticulate pigmentary disorder (XLPDR), and prurigo pigmentosa (active phase).¹⁴ More specifically, the early lesions of prurigo pigmentosa are characterized by the presence of spongiosis. The histopathological picture may vary, ranging from the presence of scattered neutrophils in the epidermis to poorly formed microabscesses to large collections of neutrophils beneath the cornified layer.^{19,20} In later stages, the infiltrate may assume a patchy lichenoid pattern and the epidermis may become hyperplastic, hyperkeratotic, and hyperpigmented. Finally, marked melanin incontinence, accompanied by the presence of melanophages in the dermis, is observed.¹⁴ The histopathological features of DKC resemble those of conditions such as graft versus host disease. However, these features may vary depending on the subtype of DKC. In patients with DKC3, interface dermatitis (lichenoid reaction), melanin incontinence, and epidermal atrophy may also be present.¹⁴ XLPDR exhibits mostly nonspecific histopathological

Table 18.1 Summary of disorders presenting with reticular hyperpigmentation.

Diseases presenting with reticular hyperpigmentation in childhood	Distribution of lesions	Inheritance	Associated gene or locus^a
Incontinentia pigmenti (Stage 3)	Skin (localized), but the disorder also affects hair, teeth, nails, and internal organs (neurologic and ophthalmologic manifestations)	X-linked dominant	Xq28
XLPRs (affected males and carrier females)	Skin—localized (in females, hyperpigmentation along the lines of Blaschko; in males, reticular hyperpigmentation)	X-linked recessive	Xp22-p21
Reticulate acropigmentation of Dohi	Skin—localized (affects dorsal areas of the distal extremities, freckling in the facial area)	Autosomal dominant	1q21.3
Dyschromatosis universalis hereditaria	Skin—widespread (affects mainly the trunk, face, and extremities), but the disorder also affects hair and nails	Autosomal dominant; autosomal recessive inheritance has been reported	6q24.2-q25.2 (DUH1) 12q21-q23 (DUH2) 2q35 (DUH3)
Epidermolysis bullosa simplex with mottled pigmentation	Skin—widespread distribution (trunk and proximal extremities)	Autosomal dominant	12q13.13/KRT5 ^b
Dermatopathia pigmentosa reticularis	Skin (widespread), but the disorder also affects hair, teeth, nails, and eccrine glands (mucosal involvement)	Autosomal dominant	17q21.2/KRT14 ^c
Naegeli–Franceschetti–Jadassohn syndrome	Skin (widespread, face, flexural areas), but the disorder also affects hair, teeth, nails, and eccrine glands	Autosomal dominant	17q21.2/KRT14 ^c
Fanconi anemia	Skin (widespread), but the disorder also affects hair, teeth, nails, and internal organs (short stature and infections)	Autosomal recessive (99%), rarely X-linked recessive (<1%)	Depending on type (various genes)
Mitochondrial diseases	Skin (widespread), but the disorder also affects hair, teeth, nails, and internal organs—depends on type of disorder	Mitochondrial DNA mutations	Depending on type
Dyskeratosis congenita (DKC)	Skin (widespread), but the disorder also affects hair, teeth, nails, and internal organs (central nervous system and retinopathy)	X-linked recessive; autosomal dominant; recessive has also been reported, depending on the type	Depending on type
Diseases presenting with reticular hyperpigmentation in adolescence/adulthood			
Acropigmentation of Kitamura	Localized, skin—acral distribution	Autosomal dominant	15q21.3
Dowling–Degos disease (DDD)	Skin, flexural distribution (localized) but can progress to generalized	Autosomal dominant	12q13.13/KRT5 ^b (DDD1) 20q11.21 (DDD2) 17q21.3-q22 (DDD3) 3q13.33 (DDD4)
Galli–Galli disease	Localized, skin—flexural distribution (a rare variant of DDD)	Autosomal dominant but can occur sporadically	KRT5 gene affected similarly to DDD1 ^b
Atopic dermatitis “dirty neck”	Localized, skin—flexural distribution	Acquired, secondary to atopic dermatitis	N/A

(Continued)

Table 18.1 (Continued) Summary of disorders presenting with reticular hyperpigmentation

Diseases presenting with reticular hyperpigmentation in childhood	Distribution of lesions	Inheritance	Associated gene or locus ^a
Lichen planus pigmentosus	Localized, skin—flexural distribution (also face and neck)	Unknown etiology	N/A
Confluent and reticulate papillomatosis of Gougerot and Carteaud	Localized, skin—mainly truncal distribution (lesions can be maculopapular)	Acquired; can be secondary to endocrine disorders, amyloidosis, reaction to fungi and bacteria, etc.	Unknown
Erythema ab igne	Localized—skin	Acquired; secondary to topical application of heat	N/A
Ashy dermatosis—erythema dyschromicum perstans	Skin, localized—mainly truncal distribution (can also affect the arms, face, and neck)	Unknown etiology	N/A
Systemic sclerosis	Skin (widespread, but shows predilection for the trunk); the disorder also affects numerous internal organs and presents with a variety of cutaneous lesions	Unknown	N/A
Pigmentatio reticularis faciei et colli	Skin, localized—main distribution on the face and neck area	Unknown; may present a variant of DDD	Unknown
• Drug-induced reticulate pigmentation	Localized—skin	Acquired	N/A
• Pigmented contact dermatitis			
• Postinflammatory hyperpigmentation			
Prurigo pigmentosa	Skin, localized (truncal distribution), associated with pruritus	Unknown	N/A

Source: Vachiramon V, *Clinical and Experimental Dermatology*, 36(5):459–66, 2011; Sardana K et al., *Indian J Dermatol Venereol Leprol*, 79(1):17–29, 2013; Muller CS et al., *Eur J Dermatol*, 22(5):596–604, 2012; Anderson RC et al., *Pediatr Dermatol*, 22(2):122–26, 2005; Swinney CC et al., *Ophthalmic Surg Lasers Imaging Retina*, 46(6):650–57, 2015; Yadalla HKK et al., *Indian Journal of Human Genetics*, 19(4):487–90, 2013; Gomes J et al., *Case Rep Med*, 2011:703257, 2011; Zaynoun S et al., *Int J Dermatol*, 47(6):542–44, 2008; Muller CS et al., *J Cutan Pathol*, 36(1):44–8, 2009; Savage SA, Dyskeratosis Congenita, in *GeneReviews*[®], ed. RA Pagon et al., Seattle: University of Washington, 1993; Mohana D et al., *Indian Journal of Dermatology*, 57(1):42–4, 2012; Desbois AC and Cacoub P, *Autoimmun Rev*, 15(5):417–26, 2016; Beutler BD et al., *Am J Clin Dermatol*, 16(6):533–43, 2015.

Note: N/A, not applicable.

^a Data acquired from the OMIM database (www.ncbi.nlm.nih.gov/omim).

^b Disorders that share genetic loci (KRT5).

^c Disorders that share genetic loci (KRT14).

features that include increased epidermal melanin, pigment incontinence with dermal melanophages, and dyskeratosis.²¹ Interestingly, XLPDR was previously referred to as “familial cutaneous amyloidosis” due to the presence of amyloid deposits in the dermis of adult patients. However, there are no other similarities between amyloidosis and XLPDR.²¹

DISEASES PRESENTING WITH RETICULAR HYPERPIGMENTATION IN CHILDHOOD

Diseases presenting with localized distribution of reticulate hyperpigmentation

Reticulate acropigmentation of Dohi (OMIM: 127400)

Reticulate acropigmentation of Dohi (also referred to as DSH) is a rare genodermatosis that is inherited as an

autosomal dominant trait with high penetrance. In general, the disorder has been found to affect individuals from Europe, India, or the Caribbean, with most of the reported cases originating in Japan.²² The exact incidence of the disease is unknown.¹⁵

DSH is caused by a mutation in the adenosine deaminase, RNA-specific gene (*ADARI*). *ADARI* protein is believed to play an important role in several processes, including virus inactivation (e.g., measles virus, HIV, and hepatitis C virus), regulation of innate immune response functions, and alteration of properties of various neurotransmitter receptors.^{15,23,24} Electron microscopic findings in the hypopigmented areas suggest increased cellular apoptosis, while melanosomes appear to be scattered, smaller than normal, and immature.²⁵ It could be

that melanocytes harboring the *ADARI* mutation are more prone to apoptosis when specific stress factors are present (e.g., viral infection).¹⁵ This could lead to the initial appearance of the typical hypopigmented lesions.¹⁵ However, the exact pathogenetic mechanism of DSH has not been fully elucidated, and it could be considered that other factors besides the *ADARI* mutation may be responsible for the phenotypic appearance of the disorder.²⁵

The condition is limited on the skin and is characterized by the progressive appearance of hyper- and hypopigmented macules, intermingled to produce a reticular pattern, located on the dorsal areas of the distal extremities.^{15,26} Ephelide-like macules may also be present on the face. The initial lesions are hypopigmented macules that start appearing during infancy or early childhood, followed by the progressive appearance of scattered hyperpigmented macules within the hypopigmented regions. In general, new lesions stop forming after adolescence. These lesions usually persist for life.¹⁵ Differential diagnoses include reticulate acropigmentation of Kitamura (RAK), xeroderma pigmentosum, and dyschromatosis universalis hereditaria (DUH).

The condition does not respond to treatment with corticosteroids. Various authors, however, have reported cosmetic improvement of lesions after surgery with split-thickness autografts or miniature punch grafting, followed by therapy with an excimer laser.^{27,28}

X-linked reticulate pigmentary disorder (OMIM: 301220)

XLPDR is a very rare genodermatosis that is inherited as an X-linked trait. Until now, only six families and one sporadic case of XLPDR have been reported, and therefore the incidence of the condition remains unidentified.²⁹ The exact pathogenetic mechanism has not yet been clarified, but genetic linkage studies have mapped the disorder to a 4.9 Mb interval in Xp22.11-p21.3.³⁰

Since XLPDR is an X-linked disorder, the manifestations between male and female patients differ, with female patients being less severely affected.⁴ However, even female patients may exhibit a dominant phenotype at the cellular level as a result of functional mosaicism due to lyonization.³¹ In female patients, the manifestations of the disease start to appear at birth or within the first few weeks of life and are usually confined to the skin. More specifically, reticulated areas of hyperpigmentation that are distributed on the lines of Blaschko and that clinically resemble the lesions appearing in cases of Stage 3 IP are typically observed. Until now, no female patients exhibiting systemic manifestations have been reported; however, mild onychodystrophy corresponding to the pigmentary lesions may be observed.^{29,32} In male patients, the manifestations of the disease start appearing between 4 months and 5 years of age.²⁹ The lacy reticulate hyperpigmentation that is typically observed does not follow the lines of Blaschko, as is the case with female patients, and is more widespread, affecting the buttocks, the inner thighs, and/or the face.^{4,33} Male patients with XLPDR may present with specific facial features that include a dysmorphic face with an upswept frontal hairline and arched eyebrows. Silvery-gray hair in fair-skinned patients and dental

anomalies have also been reported.^{4,21,33,34} Systemic manifestations that have been reported in patients with XLPDR include low birth weight, various gastrointestinal disorders (neonatal colitis and gastroesophageal reflux), failure to thrive during infancy, photophobia (due to corneal dyskeratosis), recurrent infections (e.g., pneumonia), neurological disorders (seizures and hemiplegia), chronic obstructive pulmonary disease, hypohidrosis, skeletal disorders, urethral strictures, and inguinal hernias.^{4,21,29,33,34} The possible differential diagnoses differ depending on the gender of the affected individual and include dyskeratosis congenita and NFJS for males. In both males and females, most of the conditions that are associated with reticulate hyperpigmentation should be considered (Table 18.1).

There are no specific treatment options for the disorder, and therefore, supportive care is recommended. Genetic counseling for families with one child affected by XLPDR and planning future pregnancies should be strongly encouraged.

Incontinentia pigmenti (OMIM: 308300)

IP is a rare multisystem genodermatosis that is inherited as an X-linked trait and is caused by loss-of-function mutations in the *IKK-gamma* gene (*IKBKG*; 300248), also called *NEMO*, located on chromosome Xq28.³⁵ The condition is usually antenatally lethal for male patients, and therefore more than 95% of affected individuals are females.^{18,36} The exact incidence of the condition is unknown, although cases have been reported in all ethnic groups. The pathogenesis of IP is not well understood. However, *NEMO* is a well-known modulator for NF- κ B. Therefore, it would not be unlikely that a failure to activate NF- κ B, due to the absence of the *NEMO* protein, could lead to tumor necrosis factor- α (TNF- α)-induced apoptosis of cells. This theory could, in part, explain the typical characteristics seen in IP, such as male lethality and the gradual destruction of epidermal cells. In addition, cells expressing the mutated X chromosomes are selectively destroyed after birth, while later in life, normal X chromosomes are observed in unaffected areas and mutated X chromosomes are observed only in affected areas.^{18,37}

IP is characterized by three clinical stages regarding its cutaneous manifestations. In general, the cutaneous lesions are present at birth, or appear within the first 2 weeks of life, while the systemic manifestations occur at a later time, during infancy or early childhood. During the first stage, linear erythema and blisters are observed in an otherwise healthy girl.³⁸ The lesions are vesiculobullous in appearance and are located more commonly on the limbs, trunk, and scalp and less commonly on the area of the face. The fluid extracted from these vesicles contains a high amount of eosinophils, a finding considered pathognomonic for IP.^{36,38} The vesicular lesions are present in >90% of patients with IP and resolve within a few days to weeks to be replaced by linear plaques that are more verrucous in appearance.³⁶ These lesions are typical of the second stage of IP, are most commonly located on the extremities, and are present in 70%–80% of IP patients.³⁶ During the third stage of IP, the verrucous lesions gradually disappear and are replaced by streaks and whorls of reticulate hyperpigmentation.^{18,36} These lesions

are present in almost all patients with EP (90%–98%) and are usually located on the trunk and flexural areas. These lesions tend to fade with time and are replaced in adolescence (Stage 4) by linear hypopigmented streaks lacking hair and sweat glands, usually located on the posterior areas of the limbs (e.g., the calves).³⁶ Other cutaneous manifestations of IP include hair abnormalities (lusterless, wiry, coarse hair), scarring alopecia (present in 28%–38% of patients), the absence or hypoplasia of the eyebrows and eyelashes,³⁹ dystrophic nails (pitting or ridging of the nail plate, subungual hyperkeratosis, and onycholysis), and painful subungual and periungual keratotic tumors.^{36,40}

The systemic manifestations of IP include bony deformities, skull deformities, scoliosis, lytic lesions of bones, permanent dental abnormalities (delayed eruption of dentition, partial anodontia, hypodontia, conical teeth, and dental malocclusion), oral anomalies (e.g., cleft palate),⁴¹ ophthalmologic abnormalities (such as optic nerve atrophy, loss of visual acuity, and blindness), retinal manifestations (i.e., retinal detachment, proliferative retinopathy, fibrovascular retrolental membranes, foveal hypoplasia, vitreous hemorrhages, and atrophy of the ciliary body), strabismus, microphthalmia, vortex keratitis, cataracts, iris hypoplasia, nystagmus, uveitis,⁵ and neurologic abnormalities (seizures, periventricular and subcortical white matter disease, hypoplasia of the corpus callosum, cerebral atrophy, cerebellar hypoplasia, mental retardation, ataxia, spastic paralysis, microcephaly, porencephaly, and periventricular cerebral edema).^{36,42} The criteria for the diagnosis of IP are listed in Table 18.2.^{18,43}

Table 18.2 Diagnostic criteria for incontinentia pigmenti.

Major criteria	Minor criteria
• Neonatal vesicular rash with associated eosinophilia • Hyperpigmentation on the trunk with Blaschkoid distribution, fading in adolescence • Linear, atrophic hairless lesions	• Dental anomalies • Alopecia • Abnormal nails • Ocular anomalies • Central nervous system anomalies • Abnormal hair (sparse hair, woolly hair, and anomalies of eyebrows and eyelashes) • Palate anomalies • Multiple male miscarriages • Typical skin pathohistological findings

Conditions for establishing the diagnosis of IP

- No evidence of IP in a first-degree female relative: At least two or more major criteria or one major and one or more minor criteria are necessary to make a diagnosis of sporadic IP.
- In cases of confirmed IKBKG mutation typical for IP: Any single major or minor criterion is satisfactory for IP diagnosis.
- Evidence of IP in a first-degree female relative: Any single major or at least two minor criteria.

Source: Minic S et al., *Clin Genet*, 85(6):536–42, 2014; Landy SJ and Donnai D, *J Med Genet*, 30(1):53–9, 1993.

The possible differential diagnoses for IP depend on the stage of the condition. During Stage 1, IP should be differentiated from conditions such as bullous impetigo, herpes simplex, varicella, epidermolysis bullosa, bullous mastocytosis, linear IgA (immunoglobulin A) bullous disease of childhood, Langerhans cell histiocytosis, erythema toxicum, miliaria, and arthropod assault, among others. During the second stage, other possible diagnoses include linear epidermal nevus, lichen striatus, X-linked dominant chondrodysplasia punctata, and verruca vulgaris. During the third stage of the disease, differential diagnoses should be made from linear and whorled nevoid hypermelanosis, pigmentary mosaicism, dermatopathia pigmentosa reticularis (DPR), NFJS, and X-linked dominant chondrodysplasia punctata, while in the fourth stage of IP, differential diagnoses include hypomelanosis of Ito (IP achromians), Goltz syndrome, and X-linked dominant chondrodysplasia punctata.

In general, treatment of IP should be symptomatic. Frequent ophthalmologic, neurologic, and dental examinations are highly recommended. In addition, genetic counseling for affected families may be beneficial in planning future pregnancies. The cutaneous manifestations do not require special attention, although in some instances the use of topical corticosteroids or tacrolimus may hasten the resolution of lesions in Stages 1 and 2 of the disease.^{44,45}

Diseases presenting with widespread distribution of reticulate hyperpigmentation

Dyschromatosis universalis hereditaria

DUH is a rare genodermatosis that has been shown to affect primarily the Japanese. Three types of the disease have been described until now: DUH type 1 (OMIM: 127500), mapped on 6q24.2–q25.2 and inherited as an autosomal dominant condition⁴⁶; DUH type 2 (OMIM: 612715), mapped on 12q21–q23 with an unclarified manner of inheritance (autosomal recessive?)⁴⁷; and DUH type 3 (OMIM: 615402), mapped on 2q35 and inherited in an autosomal dominant manner.^{46,48} Sporadic cases of DUH have also been reported.⁴⁹ The reticulate acropigmentation of Dohi is considered by some authors as a localized form of DUH.

Most of the patients suffering from DUH develop the characteristic reticular pigmentation during infancy or in early childhood (before the age of 6 years).^{6,50} Numerous irregularly shaped asymptomatic hyper- and hypopigmented macules can be found during birth (less than 20% of cases) or gradually appear on the back and the extremities of patients, including the dorsal areas of the hands and feet, and usually sparing the palms and soles.^{48,51} The area of the face may also be involved in about 50% of patients.⁵² Hair and nail abnormalities have been rarely reported, while the mucous membranes remain unaffected.⁴⁶ In most cases, no systemic involvement is reported; however, there have been some isolated cases of eye abnormalities (glaucoma or cataract), deafness, short stature, hematological abnormalities, renal failure, seizures, tryptophan metabolism irregularities, and adematoglyphia.^{53–55}

There are no specific treatment recommendations for DUH; however, some authors have advocated the use of nbUVB (narrowband ultraviolet B radiation).⁶

Epidermolysis bullosa simplex with mottled pigmentation (OMIM: 131960)

Epidermolysis bullosa simplex with mottled pigmentation (EBSMP) is an extremely rare genodermatosis that belongs to the spectrum of the epidermolysis bullosa simplex disorders. It is inherited as an autosomal dominant trait and is caused by a heterozygous mutation in the keratin 5 gene (*KRT5*; 148040) on chromosome 12q13.^{56,57} The exact pathogenetic mechanism of the condition is not fully understood. However, it could be possible that a mutation in *KRT5* could lead to the production of abnormal keratin filaments, associated with an aberrant melanosome uptake.^{58,59}

The disorder is characterized by clinical heterogeneity regarding skin manifestations and the age of presentation.⁶⁰ The coexistence of additional features, such as dental abnormalities, nail disorders, photosensitivity, and telangiectasias, has been rarely reported.⁶⁰ The appearance of bullae is usually the first clinical manifestation of EBSMP. Bullae are usually observed at birth or during early infancy, affect most commonly the distal extremities, and heal without scarring or milia formation.^{56,57} However, there have been some rare reports of generalized blistering.⁶¹ The tendency for bullae formation decreases with age.⁶⁰ The typical reticular pigmented lesions appear during late infancy or early childhood and consist of multiple hypo- and hyperpigmented lesions that affect most commonly the extremities and the trunk and less commonly the intertriginous areas.⁶⁰ In some cases, hyperkeratotic lesions on the palms and soles, increased bruisability of the limbs, and longitudinally curved nails can also be observed.⁶²

Dermatopathia pigmentosa reticularis (OMIM: 125595)

DPR is a rare genodermatosis that is inherited as an autosomal dominant trait and is caused by mutations in the

keratin 14 gene (*KRT14*) that is mapped on chromosome 17q21.2. Interestingly, DPR shares this genetic locus with another reticulate hyperpigmentation disorder, NFJS (described below); both of the conditions are regarded as allelic ectodermal dysplasias and, by some, as variations of the same genetic defect.⁶³

DPR is characterized by the triad of widespread reticular pigmentation, nonscarring alopecia, and mild onychodystrophy.⁶⁴ In some cases, the nail involvement may lead to pterygium formation.⁶⁴ The earliest manifestation of the disorder is the occurrence of a mottled hypo- and hyperpigmented reticular pigmentation that appears at birth or during infancy (before the second year of life).⁶⁵ The hyperpigmentation affects mainly the trunk and the proximal extremities and persists for life. Other manifestations of DPR include adermatoglyphia, hypohidrosis or hyperhidrosis, palmoplantar hyperkeratosis (most commonly punctate palmoplantar keratoderma), darkly pigmented nipples, thin eyebrows, sparse pubic and axillary hair, and the occurrence of blisters on the dorsal area of distal extremities that heal without scarring.^{64–66} Differential diagnoses are similar to those of NFJS and are discussed in Tables 18.3 and 18.4. There are no specific treatment options for the condition besides the symptomatic management of associated manifestations. Palmoplantar hyperkeratosis may improve with the use of topical retinoic acids or keratolytics. In addition, cold compresses may assist in faster healing of nonscarring blisters that are otherwise transient in nature.⁶⁵

Naegeli–Franceschetti–Jadassohn syndrome (OMIM: 161000)

NFJS is a very rare genodermatosis that is inherited as an autosomal dominant trait and is caused by a heterozygous mutation in the keratin 14 gene (*KRT14*) on chromosome 17q21.⁶⁷ The exact pathogenesis of the disorder has not yet been fully elucidated. However, some authors have suggested that the causative mutations on *KRT14* may lead to increased susceptibility of keratinocytes to apoptosis,

Table 18.3 Summary of the characteristics of DPR and NFJS.

	DPR	NFJS
Pigmentation	• By second year of age • Affects trunk and proximal extremities • Persistent in adulthood	• By second year of age • Affects abdominal, trunk, perioral, periorcular, proximal extremities, and intertriginous areas • Greatly improves after puberty
Nails	Mild onychodystrophy	Onycholysis, subungual hyperkeratosis, malalignment of the great toenails
Hair	Nonscarring alopecia, thin eyebrows	Not affected
Teeth	Not affected	Supernumerary teeth, abnormal tooth enamel, malformed teeth
Dermatoglyphs	Decreased or absent	Decreased or absent
Sweat glands	Hypohidrosis or hyperhidrosis	Hypohidrosis and heat intolerance
Palmoplantar keratoderma	Present	Present

Source: Vachiramon V, *Clin Exp Dermatol*, 36(5):459–66, 2011; Shanker V and Gupta M, *Indian Dermatol Online J*, 4(1):40–2, 2013; Itin PH et al., *J Am Acad Dermatol*, 28(6):942–50, 1993; Tubaigy SM and Hassan HM, *J Forensic Sci*, 59(2):555–8, 2014.

Table 18.4 Possible differential diagnoses for NFJS and their distinguishing features.

Disorder	Distinguishing features
Dermatopathia pigmentosa reticularis	• Discussed in Table 18.2
Dyskeratosis congenita	• Leukoplakia • Bone marrow failure • Increased risk of malignancies
Incontinentia pigmenti	• Pigmentation appears after inflammatory phase • Follows lines of Blaschko
X-linked reticulate pigmentary disorder	• X-linked trait • Systemic manifestations
Epidermolysis bullosa simplex with mottled pigmentation	• Blistering is the presenting symptom and is prominent

Source: Pezzani L et al., *Am J Med Genet A*, 161a(6):1414–20, 2013; Geller L et al., *Pediatr Dermatol* 30(5):631–2, 2013; Glasz-Bona A et al., *Eur J Dermatol* 20(6):698–700, 2010; Savage SA et al., *Pediatr Blood Cancer* 53(3):520–3, 2009.

induced by exposure to TNF- α . This could in part explain the appearance of hyperpigmentation following the pigment incontinence typically observed in patients with NFJS.⁶⁸ It is uncertain whether any similarities in the pathogenetic mechanisms of NFJS and DPR exist.

Similarly to DPR, the earliest manifestation of the disorder is the appearance of mottled hypo- and hyperpigmented macular areas that develop by the second year of life, and affect mainly the abdominal, periocular, and perioral areas. Involvement of the neck, trunk, proximal extremities, axillae, and groin has also been reported. The hyperpigmentation improves with time, and in most cases, it fades or even completely disappears after puberty.⁶⁹ Other manifestations of the disorder include hypohidrosis and heat intolerance; adermatoglyphia (or decreased dermatoglyphics); palmoplantar keratoderma; nail abnormalities, such as onycholysis, subungual hyperkeratosis (brittle nails), and congenital malalignment of the big toenails; dental anomalies (with typically defective tooth enamel characterized by a rough surface and yellow spots); and supernumerary or abnormally shaped teeth. In addition, there have been some cases where bullae occurrence on the feet of infants has been reported.^{1,69,70} A summary of the features in DPR and NFJS can be seen in Table 18.3.^{1,65,69,70} No specific treatment options exist for the disorder, and the possible differential diagnoses are discussed in Table 18.4.^{29,56,57,71}

Dyskeratosis congenita

More than 10 different mutations have been reported in association with DKC. The condition can be inherited as an X-linked trait (DKC1, OMIM: 305000), mapped on chromosome Xq28, which encodes the DKC1 protein (dyskerin 1), as an autosomal dominant trait (3q26.2, 5p15.33, 14q.12, 16q22.1, and 20q13.33), or as an autosomal recessive trait (5p15.33, 5q35.3, 15q14, 16p13.12, 16q22.1,

17p13.1, and 20q13.33).^{72–74} The X-linked type of DKC is considered to be the most common subtype, and therefore the majority of affected patients are male (3:1). In all different genotypes, the telomerase activity is decreased, and affected patients present with shortened telomeres. More specifically, in the X-linked type of DKC, the dyskerin protein, an important part of the telomerase complex, is not appropriately produced. Similarly, in DKC with autosomal dominant and recessive type of inheritance, mutations affecting the *TERT*, *TERC*, and *NOP10* genes (among others) are observed.⁷³

In general, telomeres are DNA protein structures that extend for thousands of bases at chromosome ends. During DNA replication, a gradual shortening of telomeres is observed, with subsequent cycles, due to the fact that DNA replication mechanisms are, by definition, unable to correctly copy end DNA. This process is highly regulated and eventually leads to cell senescence.⁷⁵ Telomerase and the shelterin complex constitute protective mechanisms against premature telomere erosion. On one side, the shelterin complex physically protects telomeres, and on the other side, telomerase (composed of TERT, a reverse transcriptase, and TERC, an RNA fragment that acts as a template for telomere addition) protects telomeres by elongating them. Mutations affecting shelterin or telomerase activity may lead to the appearance of premature aging syndromes or various malignancies.⁷⁵

DKC is characterized by a wide variety of symptoms. Typical features of the disorder include the triad of reticulated hyperpigmentation, nail dystrophy, and leukoplakia, usually accompanied by bone marrow failure.⁷¹ In addition to these, a number of other manifestations might be present. These include teeth abnormalities (malformation, aberrant spacing, or extensive caries), continuous lacrimation (due to lacrimal duct atresia), increased risk for hematological malignancies (myelodysplasia, acute myelogenous leukemia, and Hodgkin's lymphoma), immunological deficiencies, developmental delay, testicular atrophy, liver cirrhosis, pulmonary fibrosis, and an increased risk for a variety of carcinomas (including squamous cell carcinomas of the oral cavity, anus, cervix, vagina, esophagus, and skin and gastrointestinal carcinomas).⁷¹ A subtype of DKC, Revesz syndrome, has been additionally associated with neurological manifestations, such as intracranial calcifications, exudative retinopathy, and progressive neurological deterioration. Bone marrow failure is considered a very common feature of DKC, affecting the majority of patients and occurring during the second or third decade of life.⁷¹ In order for a diagnosis to be made, two of the four major features of the mucocutaneous triad and bone marrow failure and two or more of the other somatic symptoms should be present. Early diagnosis of the condition is extremely important since the prognosis is grave, with most patients dying (on average) by the age of 16 due to bone marrow failure, malignancy, pulmonary complications, or opportunistic infections.⁷¹

The most typical cutaneous manifestation of DKC is the appearance of a gray to tan-colored mottled, reticulated

pattern of hyperpigmentation that affects mainly the superior part of the chest, the neck, and the upper arms and develops during the first decade of life. The cutaneous manifestations of DKC clinically and histopathologically resemble those seen in patients with graft versus host disease. Thinning and early graying of hair, hyperkeratosis of palms and soles, adermatoglyphia, acrocyanosis, telangiectasias, and poikiloderma have also been observed.⁷¹ Some authors have suggested that these patients may also be at increased risk for the development of skin cancer.⁷⁶ Mucosal manifestations include the occurrence of premalignant oral leukoplakia, appearing during adolescence and affecting most commonly the lateral portions of the tongue (associated with an increased risk of oral malignancy).^{71,76} Nail abnormalities usually appear during early childhood and include longitudinal ridging, splitting, and pterygia formation that may lead to complete nail loss.⁷¹

Differential diagnoses of DKC include Fanconi's anemia, NFJS, and DPR (Tables 18.3 and 18.4). In addition, graft versus host disease may present with similar skin manifestations but usually occurs in association with a previous history of hematological malignancy or stem cell transplantation.

The appropriate approach for patients affected by the disorder is multidisciplinary and requires planning of a rigorous follow-up. Annual exams by a dermatologist are strongly recommended, with recommendations for limited exposure to the sun, sunscreen use, and avoidance of smoking. The oral mucosa should be examined annually, while a biannual dental exam is strongly recommended. In addition, the patients must be evaluated at regular intervals by a hematologist, gastroenterologist, ophthalmologist, and number of other specialties, depending on the manifestations of the DKC.⁷¹

DISEASES PRESENTING WITH RETICULAR HYPERPIGMENTATION IN ADOLESCENCE OR ADULTHOOD

Diseases presenting with localized distribution of reticulate hyperpigmentation

Acropigmentation of Kitamura (OMIM: 615537)

RAK is a rare genodermatosis that is inherited in an autosomal dominant manner, and is caused by mutations on the *ADAM10* gene, mapped on chromosome 15q21.3.⁷⁷ The exact incidence of the condition is unknown. In general, cases have been reported in association with most ethnic backgrounds; however, the vast majority of patients are of Japanese origin.⁷⁷ A number of authors have suggested that RAK should be considered a variant of DDD; however, this remains highly controversial, as the two disorders are caused by different gene mutations and exhibit distinct phenotypes. In RAK, loss-of-function mutations in *ADAM10* are commonly observed.⁷⁷ The *ADAMs* are considered a new gene family that belong to the zinc protease superfamily.^{78,79} More specifically, *ADAM10* has been shown to play a role in the ectodomain shedding of various substrates in the skin, such as the L1 cell adhesion molecule (L1-CAM), CD44, E-cadherin, N-cadherin,

IL-6R, and CD30.⁸⁰ At this point, the exact pathogenetic mechanism of RAK is not well understood, but *ADAM10* haploinsufficiency was recently reported to cause freckle-like macules in specific murine models.⁸¹

The typical manifestations of RAK include the appearance of a reticulate hyperpigmentation and pitting on the palms, soles, and dorsal phalanges. The disorder appears during late childhood (usually before the age of 20 years) as slightly depressed macular reticulate hyperpigmented areas, without hypopigmentation, located on the dorsal aspects of the hands and feet.^{3,77} The reticulate pigmentation may become more prominent with older age and may expand to affect the proximal areas of the extremities as well.¹ The disorder usually stops progressing when the patients reach middle age, after which the clinical manifestations remain stable.^{1,77} Fissuring in the epidermal ridges on the palms and fingers, breaks in the dermatoglyphics, plantar keratoderma, and partial alopecia have also been reported in association with RAK.^{77,82} Differential diagnoses include common solar lentigines; however, lentigines tend to appear at older ages and are not associated with atrophy, DSH (but in DSH, hypopigmentation is also present), or DDD, which exhibits a different distribution pattern of lesions.

The patients must be informed that sunlight may aggravate the condition. The possible treatment options are similar to those used in DDD and include the use of topical hydroquinone, tretinoin, adapalene, and corticosteroids. Some authors have advocated the use of the erbium:YAG laser and intense pulsed light as being beneficial.^{83,84}

Dowling–Degos disease (OMIM: 179850)

DDD is an uncommon genodermatosis that is inherited as an autosomal dominant trait and is usually caused by a mutation in the *KRT5* gene, located on chromosome 12q13.13.⁸⁵ However, DDD has been associated with mutations in other genetic loci, such as 17q21.3-q22, 20q11.21, and 3q13.33.^{85–88} All genotypes of DDD present with similar clinical features. EBSMP and GGD are also caused by mutations in the *KRT5* gene, but until now, the reason for the marked phenotypic differences between the diseases remains unknown.

Cases of DDD have been reported in association with almost all ethnic groups, and men and women are equally affected. In general, DDD is considered to be a result of loss-of-function mutations in the keratin 5 gene (*KRT5*), leading to haploinsufficiency. Some authors suggest that the mutated area on keratin 5 is able to interact with heatshock protein 70 (Hsc70), a chaperone involved in vesicle uncoating, and therefore influence normal melanosome trafficking.⁸⁵ The importance of the keratin intermediate filament cytoskeleton within basal keratinocytes in epidermal pigment biology has been demonstrated by other studies as well.⁸⁹

DDD usually presents during the third or fourth decade of life as a reticulate pigmentation that primarily affects the flexures. More specifically, ephelide-like brown macules and small brown papules with hyperkeratosis typically occur in a reticulate pattern and, in some instances, may coexist with prominent comedo-like lesions and

Table 18.5 Possible differential diagnoses for DDD and their distinguishing features.

Disorder	Distinguishing features
Reticulate acropigmentation of Kitamura	• Appears during adolescence • Palmar pits are present • Does not affect flexures • Atrophic areas may be present
Acanthosis nigricans	• Velvety plaques, not reticulate hyperpigmentation, are the main feature
Neurofibromatosis type 1	• Café-au-lait spots present • Neurofibromas present • A number of systemic manifestations are present
Haber syndrome	• Rosacea-like facial eruption during adolescence • Reticulate hyperpigmentation affects trunk and proximal extremities
Galli–Galli disease	• Intensely pruritic papular or papulovesicular eruption is usually present

Source: Kono M et al., *Hum Mol Genet*, 22(17):3524–33, 2013; Batycka-Baran A et al., *Dermatology*, 220(3):254–8, 2010; Gilchrist H et al., *J Am Acad Dermatol*, 58(2):299–302, 2008; Nishizawa A et al., *Br J Dermatol*, 160(1):215–17, 2009.

pitted scars.⁹⁰ The lesions initially affect the axillary and groin areas, but with time, they may progress to include the intergluteal and inframammary folds, the neck, and the trunk. Pruritus of the affected areas has commonly been reported.⁹⁰ DDD has not been linked with systemic manifestations, but has been reported in association with epidermoid cysts and hidradenitis suppurativa in some patients.⁹¹ This observation may suggest a possible defect of follicular proliferation in those patients.⁹¹ The differential diagnoses of DDD are discussed in Table 18.5.^{77,90,92,93}

No specific treatment has been found effective in DDD; however, some subsets of patients may benefit from the use of topical retinoic acids, topical steroids, hydroquinone, tretinoin, systemic retinoids, erbium:YAG laser, and intense pulsed light.^{83,84,94}

Galli–Galli disease

GGD is an extremely rare genodermatosis and is considered an acantholytic variant of DDD. GGD is caused by mutations on the *KRT5* gene, similarly to DDD and EBSPM, and is believed to be inherited as an autosomal dominant trait with variable penetrance, although sporadic cases have also been reported.^{7,92} The exact pathogenesis of the disorder is not understood.

The disorder is characterized by the appearance of an intensely pruritic papular or papulovesicular eruption involving the flexures, trunk, and extremities that is associated with reticulated hyperpigmentation located in flexural areas, such as the neck and the axillary or inguinal region.⁹² The reported age of the appearance of GGD varies from 15 to 56 years.^{7,92}

Differential diagnoses should include DDD, transient acantholytic dermatosis (Grover's disease), Darier's disease, and epidermolysis bullosa with mottled pigmentation.

There are no specific treatment options for GGD, as most treatment regimens yield unsatisfactory results. However, topical steroids, topical retinoids, and nbUVB phototherapy could be beneficial in some cases.⁹²

Lichen planus pigmentosus

Lichen planus pigmentosus (LPP) is an uncommon condition that belongs to the spectrum of the lichen planus disorders, but also exhibits a strong correlation with EDP or ashy dermatosis.⁸ The condition affects men and women equally and usually presents during the third to fifth decades of life. The incidence of LPP is not known; however, it is more commonly observed in patients with darker skin color and has been more often reported in patients from the Middle East, India, and Latin America.⁹⁵ The exact pathogenesis of LPP is not understood, although a correlation with hepatitis C infection and mustard oil has been reported.^{96,97}

LPP initially presents as small, multifocal, oval macules that gradually coalesce to irregularly shaped or oval, brown to gray-brown patches that are characterized by irregular or ill-defined borders.⁹⁶ LPP can affect either the sun-exposed areas, including the forehead, the temples, and the neck area, or the intertriginous areas. In cases where the flexural areas are affected (axillae and/or groin), the disorder is defined as lichen planus pigmentosus inversus.⁹⁸ The typical LPP lesion distribution is usually symmetrical; however, linear and unilateral patterns of distribution have also been described. These include the linear/Blaschkoid and Zosteriform variants of LPP.^{96,99} In general, LPP is usually asymptomatic, but mild pruritus or burning sensation has rarely been reported. Typically, the palmoplantar areas, the nails, and the oral mucosa are not affected.^{95,96}

The differential diagnoses of LPP include the actinic and inverse variants of lichen planus, lichenoid drug eruptions, drug-induced or postinflammatory hyperpigmentation, poikiloderma of Civatte, EDP, melasma, cutaneous T-cell lymphoma, urticaria pigmentosa, and idiopathic eruptive macular hyperpigmentation.

LPP is considered a recalcitrant and persistent disorder, and therefore, at this point, there are no specific treatment options. Topical tacrolimus, topical and oral corticosteroids, retinoids, dapsone, Nd:YAG laser, and sun exposure avoidance have all been used in the treatment of LPP with variable results.^{96,100}

Confluent and reticulate papillomatosis of Gougerot and Carteaud (OMIM: 167900)

CARP is a rare disorder that affects mainly the young and presents as multiple brown papules or patches appearing in a reticulated pattern. The exact incidence of the condition is unknown, with cases, however, reported in most ethnic groups. Some authors report that CARP may be more common in patients of African American origin and in females; however, data from various studies have yielded conflicting results.^{101,102}

The exact pathogenesis of CARP has not yet been elucidated. Some authors suggest that CARP may be a disorder of keratinization, a theory supported by the fact that many patients respond to treatment with oral and/or topical retinoids.^{103,104} Another theory suggests that CARP could be caused by endocrine imbalance. This theory is supported by the fact that many patients are overweight or present with menstrual irregularities, diabetes mellitus, or pituitary or thyroid disorders. In addition, CARP exhibits a clinical resemblance to another disorder associated with endocrine imbalance: acanthosis nigricans.¹⁰³ Finally, other theories suggest that CARP may be associated with an abnormal host response to the *Malassezia furfur* yeast, a bacterial infection (*Dietzia* strain of *Actinomyces*),¹⁰⁵ or UV radiation, or that it is a variant of cutaneous amyloidosis.¹⁰³

The average age at onset has been reported to vary from 17.1 to 21 years, with the majority of patients presenting shortly after puberty.^{102,103} CARP usually presents as 1–2 mm papules, primarily affecting the intermammary, interscapular, or epigastric area. The lesions enlarge, gradually obtain a gray-brown color, and become hyperkeratotic verrucous papules (4–5 mm in diameter) that coalesce to a centrally confluent and peripherally reticulated pattern.¹⁰³ With time, the lesions may expand to involve the neck, the shoulders, and the back. The skin may become thickened and skin markings may become more accentuated.¹⁰⁶ Typically, the eruption is asymptomatic or mildly pruritic.¹⁶

In 2006, diagnostic criteria for CARP were suggested by Davis et al. These included the presence of the typical reticular pattern of scaly, papillomatous brown lesions; the involvement of the upper trunk and neck; a negative staining of scales for fungal infection; no response to antifungal treatment; and finally, an excellent response to treatment with minocycline.¹⁶ These criteria may be found useful in the early diagnosis of CARP; however, one must take into consideration that a number of patients may not have truncal involvement or may present with positive stains for *M. furfur*.

Differential diagnoses for CARP include acanthosis nigricans, which does not exhibit a reticulate pattern of pigmentation; pseudoacanthosis nigricans, whose occurrence is closely related to weight changes (weight gain); Darier disease, in which erosions and a specific characteristic odor may be present; “terra firma” or dirty skin, where lesions are easily removed with an alcohol swab; and tinea versicolor.

Various treatment regimens have been found somewhat effective in the treatment of CARP. However, in most cases, responses can be disappointing and the disorder recurs shortly after treatment cessation. Treatment options include the administration of topical (tazarotene) or oral (isotretinoin, etretinate, and acitretin) retinoids, antibiotics (azithromycin, minocycline, fusidic acid, clarithromycin, erythromycin, and tetracycline), antifungal agents (i.e., ketoconazole cream), topical salicylic acid, calcipotriene, tacalcidol, selenium sulfide, and 5-fluorouracil, among others.¹⁰³ In general, oral antibiotics such as minocycline

and azithromycin have been associated with acceptable treatment responses, can be combined successfully with various keratolytics, and are considered the first-line treatment for CARP. Treatment with retinoids has been associated with better long-term responses; however, due to their teratogenic effect and given the fact that CARP affects mainly young adults, they should be prescribed as second-line treatments and with caution.¹⁰³

Ashy dermatosis: Erythema dyschromicum perstans

Erythema dyschromicum perstans (EDP) is an asymptomatic disorder that is characterized by the appearance of well-circumscribed areas of ash-colored pigmentation. The disorder is considered rare and is usually observed in patients from Latin America (i.e., El Salvador), although cases in Europe have also been described, affecting mostly people of darker skin color.⁸ EDP can present at any age, while men and women are equally affected. The exact pathogenetic mechanism of the condition has not been elucidated. Recent studies involving patients from Latin America have identified a polymorphism on HLA-DR4 subtype *0407 that could act as a predisposing factor for EDP. More specifically, Correa et al. reported that 65% of patients with EDP were positive for the allele compared with 23% of the control group.¹⁰⁷ These results were corroborated by other authors as well.^{8,108} The exact importance of this finding is not yet understood. A variety of predisposing factors have also been reported. These include exposure (ingestion) to ammonium nitrite and x-ray contrast media, ingestion of various types of medications (e.g., benzodiazepines and penicillin), whipworm infections (nematodes), and thyroid disease. These factors may elicit, in a susceptible individual, an aberrant T-cell-mediated response that could result in melanin incontinence, and therefore the characteristic dermal hyperpigmentation observed in EDP.¹⁰⁹

In EDP, round or irregularly shaped macules and patches ranging from 0.5 to 3 cm gradually appear and affect the trunk, the neck, the proximal upper extremities, and occasionally, the face, in a symmetric manner. Typically, these lesions exhibit gray or bluish-brown pigmentation. The oral mucosa and the genitalia remain unaffected by the condition.¹⁰⁸ In some instances, the typical lesions of EDP may present with mildly erythematous borders accompanied by scaling. In a recent study, it was reported that only 17.3% of EDP cases demonstrated perilesional erythema.¹¹⁰ This distinct manifestation has led a number of authors to suggest that EDP and ashy dermatosis should be considered distinct entities, with ashy dermatosis exhibiting identical clinical manifestations as EDP, but lacking perilesional erythema.^{8,109}

In general, the hyperpigmentation observed in EDP does not improve with time, although the age of appearance may play a role in prognosis. In prepubertal cases, the clinical course may be milder, and the hyperpigmentation may disappear after 2 or 3 years, spontaneously.¹¹¹

Differential diagnoses of the condition include lichenoid drug eruption, LPP, idiopathic eruptive macular

pigmentation (although in these cases the pigmentation is brownish and not grayish in color), generalized fixed drug eruption, macular urticaria pigmentosa (pruritus is more pronounced in these cases), and infectious diseases such as leprosy or pinta.

Until this point, there are no specific treatment options for EDP, with most of the proposed regimens yielding only partial responses. Some recent case reports have suggested that topical tacrolimus¹¹² or oral isotretinoin might be effective in treating the disease.¹¹³ Other modalities include topical or oral corticosteroids (which may be more effective in patients where perilesional erythema is observed), nbUVB radiation therapy, avoidance of sun exposure, antibiotics, topical hydroquinone, antihistamines, griseofulvin, chemical peels, vitamins, isoniazid, chloroquine, dapson, and clofazimine.¹⁰⁸ Dapsone and clofazimine have shown promising results in some small case series.¹¹⁴

Prurigo pigmentosa

Prurigo pigmentosa is a recurrent dermatosis that is characterized by severe pruritus and a reticulate hyperpigmentation that occurs after the appearance of urticarial-like plaques. The exact etiology and pathogenesis of the condition remain unclear. In general, the disorder most commonly affects individuals of Asian descent and can present at different ages, ranging from 15 to 60 years (average 25–27 years), showing a marked predilection for females.^{115–117}

Typically, prurigo pigmentosa appears as urticarial papules or plaques that gradually evolve to papulovesicular lesions and then progress to become reticulated brownish macules.¹¹⁷ The urticarial and papular lesions persist for about a week before they progress to the typical residual mottled-macular reticular hyperpigmentation.¹¹⁷ However, lesions of different ages may be observed at the same time on each affected patient. These include urticarial papules and plaques, which are often scratched; papules; papulovesicles; papulopustules; crusted and scaly papules; and pigmented macules. The most frequently affected site is the trunk area (back and chest), while the proximal extremities may also be involved, although less frequently.¹¹⁷

Treatment regimens with antihistamines and topical or systemic corticosteroids are usually inefficient in the treatment of the disorder. Many authors suggest that the use of tetracyclines, such as minocycline, may be beneficial for some patients in reducing both the pruritus and the exanthem.^{118,119} Other options include dapson, potassium iodide, and macrolide antibiotics.¹¹⁶ There are no specific treatment options for the reticulate hyperpigmentation, which tends to be very persistent.¹¹⁶

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INTRODUCTION

Molecular genetics has revealed through the years that genes play a crucial role in melanocyte development and function. A single gene may be required for various functions in different cell types, and accordingly, in a pigmentation disorder, the genetic insult may cause defects not only to melanocytes but also in other types of cells.¹

In normal human epidermis, individual melanocytes are located apart from one another along the epidermal basal layer, having close by in their neighbourhood keratinocytes, Langerhans cells, fibroblasts, vascular cells, and nerve endings.²

The structural and functional grouping of a single melanocyte with a large number of surrounding keratinocytes is called the epidermal melanin unit (EMU), with the average ratio of EMU melanocytes to nucleated keratinocytes estimated at 1:36.³

When the genetic signaling is altered, there is consequently a modified architecture of the EMU, with overgrowth of melanocytes and clinically the presence of sharply demarcated pigment spots or even greater amounts of congenital hyperpigmentation, at or soon after birth.⁴

In this chapter, genodermatoses characterized by hyperpigmentation are discussed. Congenital forms of hyperpigmentation with an increased number of melanocytes include disorders with multiple lentigines and nevocellular or melanocytic nevi. On the other hand, altered genetic signaling cascades of melanogenesis may cause an increase in melanin levels, without increasing the number of melanocytes, and result in congenital disorders with extensive hyperpigmentation (Table 19.1).

DISORDERS WITH INCREASED NUMBER OF EPIDERMAL MELANOCYTES

Congenital melanocytic nevi are present at birth or soon after birth. They may be small or even extremely large (>20 cm), covering large areas. Apart from the aesthetic disfigurement, there is a melanoma risk directly connected to the size. Heritability is suggested for the giant pigmented hairy nevi.⁵

Becker nevus or *Becker melanosis* presents as a macule with irregular brown pigmentation on the chest, back, or upper arm that spreads as a patch of 10–15 cm in diameter and is progressively associated with hypertrichosis. It most commonly presents in males and in early adolescence. It may have a genetic influence in some patients, as there are some reports of familial cases.⁶

The *RASopathies* is a group of disorders arising from dysregulation of RAS-MAPK signaling and include neurofibromatosis 1 (NF1), Legius syndrome, LEOPARD syndrome,

and Noonan syndrome. The above entities have an overlapping phenotype.⁷

NF1 is an autosomal dominant genetic disorder, with a reported incidence of about 1/3000 live births. The presence of two or more of the below criteria is necessary for making a clinical diagnosis of NF1:

1. Six or more café-au-lait macules (>0.5 cm in prepubertal period, >1.5 cm in postpubertal period) (Figure 19.1)
2. Two or more neurofibromas or one plexiform neurofibroma
3. Axillary or inguinal freckling
4. Optic gliomas
5. Two or more Lisch nodules
6. Abnormalities of the skeletal system (sphenoid dysplasia and tibial pseudoarthrosis)
7. A first-degree relative with NF1⁸

Patients with NF1 also have learning disabilities and an increased risk for specific malignancies, such as malignant peripheral nerve sheath tumors, rhabdomyosarcoma, neuroblastoma, gastrointestinal stromal tumors, somatostatinomas, breast cancer, and pheochromocytoma.⁹

In *Legius syndrome* (NF1-like syndrome), a heterozygous mutation in the *SPRED1* gene is responsible for the phenotype. Individuals with Legius syndrome present with multiple café-au-lait spots with or without freckling. Diagnosis based on clinical features alone is not possible, because of the important clinical overlap with NF1. Learning disabilities, developmental delay, hyperactivity, autistic behavior, and concentration problems are frequently reported in children with Legius syndrome. On the other hand, patients do not show some associations with NF1 tumors, such as optic pathway gliomas and neurofibromas, bone abnormalities, or Lisch nodules. The intense medical surveillance that is needed for NF1 is not required in this syndrome.¹⁰

LEOPARD syndrome belongs to the familial lentiginosis syndromes, which are associated with an increased incidence of neural, endocrine, and mesenchymal tumors. The signaling pathways involved in these syndromes regulate protein kinase A (PKA), RAS-MAPK, and the mammalian target of rapamycin (mTOR). All these pathways converge to the regulation of growth, proliferation, and differentiation of many cell types.¹¹

In LEOPARD syndrome, mutations in three genes (RAS-MAPK signal transduction pathway genes)—protein tyrosine phosphatase, nonreceptor type 11 (PTPN11); v-raf-1 murine leukemia viral oncogene homolog 1 (RAF1); and v-raf murine sarcoma viral oncogene homolog B1 (BRAF)—have been revealed.

Table 19.1 Genodermatoses with hyperpigmented lesions.

Disorders with increased number of epidermal melanocytes	Disorders with increased number of dermal melanocytes	Disorders with increased melanin levels	Disorders with pigment incontinence
Congenital nevi	Mongolian spots	Dyschromatosis symmetrica hereditaria	Incontinentia pigmenti (third phase)
Becker nevus	Nevus of Ota	Dyschromatosis universalis hereditaria	Epidermolysis bullosa with mottled hyperpigmentation
Neurofibromatosis 1	Nevus of Ito	Linear and whorled nevoid hypermelanosis	Cutis tricolor
Legius syndrome		Xeroderma pigmentosum	
LEOPARD syndrome		Dyskeratosis congenita	
Noonan syndrome		Naegeli–Franceschetti–Jadassohn syndrome	
Peutz–Jeghers syndrome		Dyschromatosis ptychotropica	
Carney complex			
Xeroderma pigmentosum			
McCune–Albright syndrome			
Westerhof syndrome			
Ziprkowski–Margolis syndrome			

**Figure 19.1** Café-au-lait spot in a patient with neurofibromatosis.

Initially, in patients with LEOPARD syndrome, many light brown hyperpigmented spots (café au lait) 1–30 cm in diameter are present, while multiple lentiginos gradually develop.

Gene mutations may cause the development of multiple lentiginos and abnormalities of tissues derived from the neural crest, resulting in a combination of findings (multiple lentiginos, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness).

Noonan syndrome is an autosomal dominant disorder with an estimated incidence of 1/1000–2500 live births. Hyperpigmentation is variable (mostly café-au-lait spots). Clinically, the most constant criteria are short stature, dysmorphic facial features, congenital heart defects, and

chest deformities. Other phenotypical characteristics are thin and woolly or curly hair, hypertelorism, light blue irises, epicanthal folds, high forehead, broad depressed nasal base, posteriorly rotated ears with thickened helix, broad neck, low posterior hairline, widely spaced nipples, and chest defects.

The dysmorphic features are less pronounced in adulthood. Most children with Noonan syndrome have delayed psychomotor development. Additionally, visual abnormalities (strabismus, myopia, nystagmus, or hypermetropia) are present in almost 95% of cases. Patients must be followed up regularly, as an increased risk for hematological malignancies is highly documented.^{8,12}

Peutz–Jeghers syndrome is a rare autosomal dominant inherited disorder, with a prevalence of 1:8,300–200,000 live births. It is caused by a germline mutation in the *STK11* gene. In this syndrome, typically mucocutaneous lentiginous macules of 1–5 mm diameter present around the mouth, in the buccal mucosa, or on the fingertips, eyelids, or soles, from the first year of life. Multiple hamartomatous intestinal polyps may occur from early childhood, with the median age of presentation at 12 years. The lifetime hazard for cancer in patients with Peutz–Jeghers syndrome is up to 93%, and a thorough and close follow-up is absolutely recommended.¹³

Carney complex (CNC) is an autosomal dominant disorder caused by inactivating mutations or large deletions of the *PRKARIA* gene. It is characterized by lentiginos, epithelioid blue nevi, cutaneous myxomas, and pigmented schwannomas, as well as ocular, cardiac, and endocrine abnormalities. More than 80% of the patients have lentiginos on the center of the face, lips, genital area, mucosa, or even everywhere on the body.

The most common noncutaneous lesions found in CNC are cardiac myxomas (in 20%–40% of the patients), which may appear early in infancy, but the median age at detection is at 20 years. The most common endocrine tumor in CNC is primary pigmented nodular adrenocortical disease (PPNAD), a cause of (adrenocorticotropin-) independent overproduction of cortisol.¹⁴

Xeroderma pigmentosum (XP) is a genodermatosis inherited by an autosomal recessive trait. Estimated incidences vary from 1 in 20,000 in Japan to 1 in 250,000 in the United States, and approximately 2.3 per million live births in western Europe.¹⁵

It is caused by one of several defects in the excision repair and/or postreplication repair mechanism of DNA.¹⁶

In consequence, the inability of epithelial cells to repair the ultraviolet (UV)-induced damage leads to an excessively increased sun sensitivity and tendency to sunburn, and the skin becomes atrophic, dry, and rough. Patients with XP have multiple actinic keratoses since childhood, pigmented seborrheic keratoses, freckles, and patchy depigmentation. An unusually increased number of lentigines may be present by the second year of age, on the nose, cheeks, forehead, and sides of the neck, sparing the area under the chin. Hypopigmented small macules are commonly seen among the lentigines, giving rise to the characteristic mottled hyperpigmented and hypopigmented phenotype known as the salt-and-pepper pattern of skin.¹⁷

All patients develop both melanocytic (melanoma) and nonmelanocytic skin tumors (squamous cell carcinomas [SCCs] and basal cell carcinomas) before the age of 20.

The median age of onset of nonmelanoma skin cancer reported in patients with XP was 8 years, in comparison with 60 years in the general population.¹⁸ There are also oral manifestations that usually involve the lips and anterior portion of the tongue and include actinic cheilitis, glossal telangiectasia, leukoplakia, and oral carcinomas.¹⁹

In the general population, SCC most frequently affects the posterolateral and ventral surfaces of the tongue and floor of the mouth, in elderly users of tobacco and alcohol, and it runs an aggressive course. In XP patients, SCC affects the tip of the tongue of persons younger than 20 years of age, and it runs a slowly progressive course.²⁰

Photophobia is very common, and other ocular abnormalities, caused by the UV-induced DNA alteration to epithelial cells of the conjunctiva, cornea, and eyelid, occur in about 40%–80% of patients with XP. Severe keratitis with corneal opacification and vascularization, loss of eyelashes, hyperpigmentation of the eyelids, and ocular neoplasms may be induced by sunlight exposure.²¹

Neurological abnormalities such as isolated hyporeflexia, progressive mental retardation, sensorineural deafness, spasticity, or seizures may be present in 20%–30% of patients with XP, with onset from the age of 2 to middle age.²²

Despite the fact that there is no cure for XP, many of its manifestations may be reduced or prevented through consistent UV protection, and life expectancy may be prolonged.

McCune–Albright syndrome (MAS) is caused by a spontaneous mutation in the *GNAS* gene, in early embryonic development. Its estimated prevalence is 1/100,000–1,000,000, with no sex and ethnic group predominance.

In patients with MAS, there are typically poly- and monostotic fibrous dysplasia, café-au-lait spots, and autonomous endocrine hyperfunction. Diagnosis is made when at least two of the above clinical features are present.²³

An autonomous hyperfunction of a variety of cells that respond to extracellular signals through activation of the hormone-sensitive adenylate cyclase system catalyzes the production of cyclic AMP, and thus explains the involvement of other endocrine organs in this syndrome (Cushing's syndrome, hyperthyroidism, and acromegaly).²⁴

Diagnosis is most often established in early childhood, but may occur at birth due to the presence of café-au-lait macules (CALMs). CALMs have irregular borders and usually respect the midline of the body, follow the developmental lines of the Blaschko pattern of embryonic cell migration, and are commonly located on the posterior neck, base of the spine, trunk, and face. Their size and location do not correlate with the extent of disease or areas of bone disease.

Patients with MAS usually seek medical attention due to precocious puberty and fibrous dysplasia.²⁵

Westerhof syndrome is an autosomal dominant genodermatosis characterized by the presence of multiple asymmetrical hyper- and hypopigmented macules and patches (1–15 cm in diameter), with no predilection sites and not confined to any dermatome. There is no mucosal involvement. Lesions are more numerous in male than female patients. Patients may have mental deficiency or retarded growth.^{26,27}

Ziprkowski–Margolis syndrome is an X-linked recessive pigmentary genodermatosis, in which there is a diffuse hypopigmentation of the skin and hair since birth, heterochromia irides, and congenital deafness. The genital region and buttocks are not involved. A leopard-like appearance develops later, as multiple hyperpigmented macules appear symmetrically inside the pigmented areas.^{28,29}

DISORDERS WITH INCREASED NUMBER OF DERMAL MELANOCYTES

The term *dermal melanocytosis* is used when there is an increased growth of melanocytes only in the dermis, which typically remain dendritic. A blue-gray hue is caused by the light scattering of the deeply situated dermal pigment. Congenital forms of dermal melanocytosis are the *nevus of Ota* (Figure 19.2), *nevus of Ito* (Figure 19.3), and *Mongolian spots*. Nevus of Ito is typically localized on the neck or shoulders, nevus of Ota is localized on the face, and Mongolian spots are localized on the sacral or gluteal area. Nevus of Ota and Ito may originate from nerve-associated, medioventral pathway melanoblasts.

Mongolian spots (Figure 19.4) are mainly prevalent in patients of Asian or African descent, and they regress in childhood.



Figure 19.2 Nevus of Ota. (Courtesy of Prof. D. Murrell.)



Figure 19.3 Nevus of Ito. (Courtesy of Prof. D. Murrell.)



Figure 19.4 Mongolian spot. (Courtesy of Prof. A. Katsarou.)

DISORDERS WITH INCREASED MELANIN LEVELS

Dyschromatosis symmetrica hereditaria (DSH) (also known as acropigmentation of Dohi) is an autosomal dominant genodermatosis in which lentigines and patchy hyper- and hypopigmentation develop on the dorsal aspect of the extremities and on the face, usually before the sixth year of life.³⁰ The palms and soles are not involved. DSH may have a psychosocial impact, as the clinical appearance is rather unpleasant.³¹

The causative mutations have been attributed to the adenosine deaminase, RNA-specific (ADAR) gene. Up to now, more than 120 mutations have been reported, mainly from East Asian countries.³²

Association of DSH with neurological disorders, such as mental deterioration, seizures, and dystonia, has been reported.^{33,34}

Dyschromatosis universalis hereditaria (DUH) is also an autosomal dominant genodermatosis in which, in about 50% of cases, there are hyperpigmented macules on the face. Hypo- and hyperpigmented macules with irregular shape are intermingled on the abdomen, trunk, and extremities, during the first year of life.³⁵ Palms and soles may rarely be involved. The specific mutations have been detected in *ABCB6* genes.³⁶ Recently, an autosomal recessive form of DUH with later onset and stabilization of the disease over time has been described.³⁷

Comorbidities associated with DHU are short stature, photosensitivity, teeth abnormalities, deafness, and cataracts.³⁸

Familial progressive hyperpigmentation and *familial progressive hyper- and hypopigmentation* are characterized by a generalized pigmentation and are both associated with gain-of-function mutations in *KITLG*.³⁹

Linear and whorled nevoid hypermelanosis (LWNH) (Figure 19.5) is a condition characterized by hyperpigmented reticulate streaks and whorls following the lines of Blaschko, without a preceding inflammatory event or palpable lesion and sparing of mucosal surfaces and the palms and soles.⁴⁰

LWNH is assumed to reflect an underlying mosaicism or a highly variable genetic defect.⁴¹

Several mosaic chromosomal abnormalities have been documented in LWNH, including mosaic trisomies 4, 7, 18, and 20.⁴²



Figure 19.5 Linear and whorled nevoid hypermelanosis.

Age of onset is usually within the first 2 years of life.

In a number of LWNH cases, extracutaneous abnormalities have also been observed, including developmental and growth retardation, facial and body asymmetry, ventricular septal defect, and pseudohermaphroditism.⁴³

The most intriguing differential diagnosis to LWNH is hypomelanosis of Ito (HI) (Figure 19.6), in which the lesions follow the same pattern of distribution and occur at the same age. A clinical clue is that in LWNH, the linear streaks are darker than the patient's normal skin, whereas in HI they are lighter than the predominant skin color.⁴⁴

Dyskeratosis congenita (DC) is a bone marrow failure syndrome, inherited by a heterogeneous pattern of inheritance, X-linked recessive, autosomal dominant, or autosomal recessive, and the age of onset is respectively 9, 4, and 7 years.

Mutations in at least 10 telomere- and telomerase-associated genes have been linked to a defective telomere maintenance, and as a consequence, patients with DC have premature telomere shortening, subsequent replicative senescence, premature stem cell exhaustion, and tissue failure.⁴⁵

An increased risk for carcinomas (oropharyngeal, gastrointestinal, and pancreatic), Hodgkin's disease, and other hematolymphoid neoplasms is reported. Clinically, there is reticulated skin hyperpigmentation with multiple hypopigmented macules on the face, neck, trunk, and shoulders. Apart from the pigmentary disorder, there are mucosal leucoplakia, nail dystrophy, skin atrophy, telangiectasias, alopecia (scalp, eyebrows, and eyelashes), premature graying, and hyperhidrosis.⁴⁶

Leucoplakia involves the buccal mucosa, tongue, and oropharynx. There is also severe periodontal destruction with gingival inflammation, bleeding, recession, and bone loss that simulate juvenile periodontitis.⁴⁷

Nail dystrophy is progressive, beginning with ridging or longitudinal splitting and resulting in rudimentary, small, or absent nails.



Figure 19.6 Hypomelanosis of Ito.

Bone marrow failure occurs in 80%–90% of patients until the third decade of life.⁴⁸

Patients with DC usually die of bone marrow failure due to a deficient capability of their hematopoietic stem cells to renew.⁴⁹

Naegeli–Franceschetti–Jadassohn syndrome is a rare autosomal dominant form of ectodermal dysplasia, in which the typical signs are lack of sweating with subsequent heat intolerance, lack of dermatoglyphics at the fingerprints, reticulate hyperpigmentation, and yellow spots on the enamel. Usually, around the age of 2, there is a preceding inflammatory stage, followed by the development of a gray-brown reticulate hyperpigmentation around the eyes and mouth, and on the neck, abdomen, chest, axillae, groin, and proximal extremities. Palmoplantar hyperkeratosis and brittle nails may also be present. The pigmentary disorders fade with age.⁵⁰

In *dyschromatosis pychotropica*, there are multiple small hypo- and hyperpigmented macules on body folds, like the neck, axillae, and inguinal folds. The pigmentary disorder progresses slowly, with extensive lesions on the trunk and extremities. There is also an association with epileptic encephalopathies.⁵¹

DISORDERS WITH PIGMENT INCONTINENCE

Incontinentia pigmenti (IP) is a rare genodermatosis that is usually fatal for male fetuses. IP is caused by mutations in the NEMO gene (IKK-gamma). The NEMO protein is one subunit of a complex multiprotein kinase that is crucial for the activation of the transcription factor NF-kappa B, essential in the regulation of inflammatory immune and apoptotic pathways.⁵²

IP has an X-linked dominant inheritance pattern and occurs in four phases along the Blaschko lines.

Each phase of IP is chronologically distinct, but it may temporarily overlap with another or not develop in some cases.⁵³

Phase I is characterized by the development of papules, vesicles, and pustules on an erythematous base, distributed linearly along the lines of Blaschko, on the trunk, extremities, head, or neck. It may be confused with herpes simplex or impetigo. In 90% of cases, the lesions occur at birth or during the first 2 weeks of life. Lesions usually disappear by the fourth month of life. In a few cases, Phase I runs in the uterus or after the first year of life.

Phase II (Figure 19.7) is characterized by verrucous plaques and warty papules along the Blaschko lines, which may or may not correspond to the distribution of the former inflammatory lesions. They disappear by the sixth month of life.

In Phase III (Figure 19.8), whorled or linear lesions with a brownish hue occur in 90%–98% of patients. Distribution does not differ from the other phases, with the addition of nipples, axillae, and groin. As has been stated before, the location of hyperpigmented lesions does not always correlate with prior cutaneous involvement during earlier phases. Pigmentation persists for many years.

In Phase IV, hypopigmentation, atrophy, and absence of hair are observed, commonly on the lower extremities.



Figure 19.7 Incontinentia pigmenti—Phase II. (Courtesy of Prof. A. Katsarou.)



Figure 19.8 Incontinentia pigmenti—Phase III. (Courtesy of Prof. D. Murrell.)

These lesions may occur during adolescence and persist through life.⁵³

Hair may be sparse, dull, and brittle. Nails are also involved in IP. Koilonychia, fragile and brittle nails, yellowish pigmentation, hyperkeratosis, and onycholysis may occur, most commonly in fingernails.⁵⁴

Ocular abnormalities in IP include pseudoglioma or retrolental fibroplasia, retinal ischemia, unilateral or bilateral blindness, optic nerve atrophy, cataracts and strabismus, ptosis, microphthalmia, blue sclera, conjunctival pigmentation, corneal alterations, iris hypoplasia, uveitis, ocular globe atrophy, nystagmus, and myopia.⁵⁵

Neurological manifestations associated with IP range from a single episode of seizure to psychomotor retardation, intellectual impairment, hemiplegia, epilepsy,

cerebellar ataxia, microcephaly, neonatal encephalopathy, encephalitis, and neonatal and childhood stroke accidents.⁵⁶

In patients with IP, there are also dental problems, such as missing teeth, conoid teeth, additional cusps in posterior teeth, and delayed tooth eruption.⁵⁷

Epidermolysis bullosa with mottled hyperpigmentation is an autosomal dominant genodermatosis in which a missense mutation in the V1 domain of the keratin 5 gene leads to the development of blisters after minimal trauma, palmoplantar hyperkeratosis, nail dystrophy, and slowly progressing reticular pigmentation.⁵⁸

This mutation is thought to produce defective keratin filaments that produce an aberrant melanosome uptake, resulting in hyperpigmented areas.⁵⁹

The reticulate hyper- and hypopigmented areas are present since infancy, do not develop at sites of previous blisters, and lessen with age but do not disappear.⁶⁰

The most commonly involved areas are the trunk and extremities, and to a lesser extent the abdomen, armpits, and groin. In some cases, hyperpigmentation may progress to most of the body's surface.⁶¹

Cutis tricolor is another congenital pigmentary disorder, in which multiple hyper- or hypopigmented macules, patches, or streaks are present on normal skin, in a Blaschko line distribution, commonly on the trunk and arms. There is an association with neuropsychiatric abnormalities and ipsilateral breast hyperplasia. *Cutis tricolor* represents a mosaicism with three genetically different cell lines.^{62–64}

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Diagnosis and Differential Diagnosis

INTRODUCTION

The skin, unlike many other organs and systems, allows the diagnosis of cutaneous diseases and changes through visual inspection.¹ However, the dermatological diagnosis sometimes requires the use of auxiliary tests and procedures, besides a detailed history and physical examination.¹ Some of these methods are inexpensive and easy to perform for outpatient care, such as Wood's light, Tzanck cytodiagnosis, and direct microscopic examination for fungi and bacteria.¹

The proper evaluation of skin hyperpigmentation adds to finding the etiology of many disorders, allowing their correct and efficient management.

CLINICAL EXAM IN HYPERPIGMENTATIONS

Cutaneous hyperpigmentations can be congenital or acquired, localized or diffuse.² The main pigment involved in hyperpigmentation is melanin, but others, such as hemosiderin, carotenes, and pigment secondary to drugs and tattoos, may also be involved.² Diseases with hyperpigmentation comprise an extensive list, as shown in Tables 20.1 and 20.2.

The meticulous dermatologic examination is essential to guiding the diagnosis, always having in mind the main differential diagnoses of hyperchromia.

ACQUIRED HYPERPIGMENTATIONS

Melasma

Melasma is a form of localized hyperpigmentation that occurs mainly on the face. The term *melas* derives from the Greek, meaning "black."^{3,4} Melasma lesions present a brownish color and predominate in Hispanic women living in tropical areas.³ Its pathogenesis is multifactorial, with the influence of hormones; pregnancy; some drugs, such as oral contraceptives and anticonvulsants; and genetic and racial predisposition. The most important factor in the pathogenesis of melasma is sun exposure. Independently of the etiology, melanocytes are functionally altered, producing an excess of melanin.^{3,5}

Three clinical patterns of facial melasma are recognized—centrofacial, malar, and mandibular—and the melanin pigment can be located in the epidermis, dermis, or both.³

When performing the clinical exam, the lesion characteristics are helpful in the diagnosis: in melasma, lesions tend to be symmetrical, with irregular or geographical borders, following one of the three patterns explained above.⁴ Besides that, examination with natural light allows some considerations: when the pigment is epidermic,

the lesion usually has a light brown color, while dermal melasma tends to have bluish-gray coloration, due to the Tyndall effect. Mixed melasma is usually dark brown.³

Skin examination under Wood's light allows a distinction between the epidermal and dermal melasma types. For the epidermal type, under Wood's lamp, the lesion becomes darker in pigmentation, increasing the contrast with the surrounding skin.^{3,4} On the other hand, the color of dermal melasma does not change when exposed to Wood's light.^{3,4} In the mixed type, the regions with pigment located in the dermis will not change, while sites with epidermal pigment will be highlighted by the ultraviolet (UV) light.^{3,4}

In patients with skin phototypes V–VI, the melanin present in the epidermis interferes with the clinical analysis, diminishing its accuracy.^{3,4}

Scales are important tools to quantify melasma severity. The Melasma Area and Severity Index (MASI) scale measures the severity of melasma in four areas: the forehead, right malar region, left malar region, and chin, which correspond, respectively, to 30%, 30%, 30%, and 10% of the total facial area. MASI assesses the percentage of area involved in each region (A), darkening of the lesions (D), and homogeneity (H). Depending on the percentage involved in each of these four areas, a specific value is given, as explained in Table 20.3. The final score ranges from 0 to 48.⁶

In 2011, Pandya and colleagues proposed a modified version of the MASI score. Assuming that only the darkness and affected area criteria would be sufficient to quantify melasma, the authors withdrew the homogeneity criteria. This modified scale ranges from 0 to 24.⁶ Software for automated MASI calculation has been described and should be available in the near future.⁷

Another measure that can be used to assess therapeutic response in melasma is the Physician's Global Assessment (PGA).⁸ It is a score developed for the subjective analysis of hyperpigmentation (Table 20.4).⁹ Photographic records prior to treatment and after it are necessary for the dynamic assessment of PGA score changes.⁹

Melasma differential diagnoses include hyper- and hypovitaminosis, which induce skin color changes; post-inflammatory hyperpigmentation (PIH); endocrine abnormalities, such as Addison disease and abnormal thyroid function; exposure to heavy metals and other chemical compounds; and the use of drugs that can cause hyperpigmentation by drug deposit or by stimulating melanogenesis.³ Actinic lichen and photosensitive dermatosis should also be part of the differential diagnoses.⁸

Table 20.1 Congenital hyperpigmentation.

Diffuse	Localized
1. Kitamura's acropigmentation	1. Nevus of Ota and Nevus of Ito
2. Dohi's acropigmentation	2. Mongolian spot
3. Dermopathia pigmentosa reticularis	3. Café-au-lait spots • Isolated • Neurofibromatosis type 1 • Associated with colorectal cancer
4. Naegeli–Franceschetti–Jadassohn syndrome	• Other genodermatoses: Neurofibromatosis types 2 and 6, Bloom syndrome, Silver–Russell syndrome, McCune–Albright syndrome, ataxia–teleangiectasia, Westerhof syndrome, Tay syndrome, Soto syndrome, Watson syndrome, agminated lentiginosis, and LEOPARD syndrome
5. X-linked reticulate pigmentary disorder	
6. Dowling–Degos disease	
7. Epidermolysis bullosa simplex with mottled pigmentation	
8. Linear whorled nevoid hypermelanosis	
9. Incontinentia pigmenti	
10. Epidermic nevus	
11. Goltz syndrome	
12. McCune–Albright syndrome	4. Becker nevus
13. Centrofacial lentiginosis	5. Nevus spilus
14. Hereditary lentiginosis	
15. Familial progressive hyperpigmentation	
16. Dyskeratosis congenita	
17. Alkaptonuria	

Table 20.2 Acquired hyperpigmentations.

Diffuse	Localized
Hyperpigmentation induced by systemic diseases • Endocrine etiology (Addison disease, Nelson syndrome, HIV endocrine dysregulation, acromegaly, POEMS syndrome, and hyperthyroidism) • Metabolic etiology (hemochromatosis, porphyria cutanea tarda, and jaundice) • Connective tissue disorders (systemic escleroderma and juvenile rheumatoid arthritis) • Nutritional (folic acid, vitamin B1 and B12 deficiencies, kwashiorkor, and carotenemia) • Neoplastic • Drug related (fixed drug eruption and minocycline hyperpigmentation) • Heavy metal deposits • Exogenous tattoo pigment • Universal acquired melanosis: Carbon baby syndrome	1. Melasma 2. Postinflammatory hyperpigmentation 3. Periorbital hyperpigmentation 4. Dermatitis papulosa nigra 5. Meadow grass disease—phytophotodermatitis 6. Flagellate dermatitis 7. Erythema dyschromicum perstans 8. Poikiloderma of Civatte 9. Acanthosis nigricans 10. Toxic melanodermitis–Riehl melanosis 11. Primary cutaneous amyloidosis (macular and lichen amyloidosis) 12. Confluent and reticulated papillomatosis 13. Lentigo simplex • Lentiginosis: LEOPARD, Carney complex, Peutz–Jeghers syndrome, Laughier–Hunziker syndrome, Cronkhite–Canada syndrome, eruptive lentiginosis, and hereditary lentiginosis 14. Solar lentigo 15. Psoralen–ultraviolet A (PUVA) lentigines 16. Freckles 17. Cutaneous mastocytosis 18. Berloque-dermatitis 19. Universal dyschromatosis 20. Prurigo pigmentosa 21. Heat induced melanosis 22. Exogen Ochronosis 23. Pregnancy

Table 20.3 MASI.

Melasma area and severity scale	
Area (A)	<10% = 1
	10%–29% = 2
	30%–49% = 3
	50%–69% = 4
	70%–89% = 5
	90%–100% = 6
Homogeneity (H)	0 = Absent
Darkness (D)	1 = Slight
	2 = Moderate
	3 = Marked
	4 = Maximum

Note: Total MASI = $0.3A_f(D_f + H_f) + 0.3A_{lm}(D_{lm} + H_{lm}) + 0.3A_{rm}(D_{rm} + H_{rm}) + 0.1A_c(D_c + H_c)$. A = Area; D = Darkness; H = Homogeneity; f = Forehead; lm = Left malar region; rm = Right malar region; c = Chin.

Table 20.4 Physician's global assessment.

Score	Description
0	Clear, except for possible residual discoloration
1	Almost clear; very significance clearance (>90%); only minor evidence of hyperpigmentation remains
2	Marked improvement; significant improvement (75%); some disease evidence of hyperpigmentation remains
3	Moderate improvement, intermediate between slight and marked improvement; 50% improvement in appearance of hyperpigmentation
4	Slight improvement; some improvement (25%); significant evidence of hyperpigmentation remains
5	No improvement; hyperpigmented condition unchanged
6	Worse, condition worse than in week 0 (zero)

Riehl melanosis: Toxic melanodermatitis

Riehl melanosis, a pigmented dermatitis caused by contact with cosmetics applied to the face, is characterized by brownish-gray spots that predominate on the forehead and temples.⁴ Lesions can also occur in other places exposed to cosmetics, such as the neck and the back of the hands.⁴ The differential diagnosis with melasma is basically by the history of contact with cosmetics and clinical presentation.⁴

Poikiloderma of Civatte

Poikiloderma of Civatte (PC) is characterized by a triad of linear telangiectasias, superficial skin atrophy, and mottled hypo- and hyperpigmentation. PC occurs predominantly on the face and the neck in patients with low phototypes (Figure 20.1).⁴ Although the pathogenesis is not fully elucidated, exposure to solar radiation is the main implicated factor. Contact with cosmetics and perfumes

**Figure 20.1** PC on the neck and chest.

with photosensitizers may also be involved in the etiology.⁴ Differential diagnoses of PC include melasma, contact dermatitis, and erythromelanosis follicularis faciei.²

Infraorbital dark circles

Infraorbital dark circles can be caused by many factors: melanin deposit, presence of superficial vessels seen by transparency, loss of volume, and prolapse of orbital fat. The differential diagnoses of dark circles caused by pigment deposition include melasma and nevus of Ota.¹⁰

The use of topical medication should be investigated, since latanoprost and other prostaglandin analogs may be associated with lipodystrophy in the eyelid region, accentuating the tear trough. This type of lipodystrophy is generally reversible upon drug cessation, if possible. In addition, prostaglandin analogs can trigger reversible hyperpigmentation of the eyelid area.¹⁰

Dark circles under the eyes can occur in patients with atopic dermatitis and contact dermatitis, as a manifestation of PIH. Fixed drug eruption, erythema dyschromicum perstans, and acanthosis nigricans (AN) are rare causes of periorbital hyperpigmentation.

Finally, the use of drugs such as penicillamine can trigger periorbital hyperpigmentation.¹⁰

Acanthosis nigricans

AN manifests by velvety, hyperchromic plaques, with symmetrical distribution, affecting the neck, axillae, and popliteal and antecubital fossa. The main subtypes are benign, obesity related (Figure 20.2), syndromic, malignant, acral, unilateral, drug related, and multifactorial. For diagnosis, a detailed medical history, including all medications taken, and a thorough physical examination for additional clinical findings are extremely important for defining the etiology. Laboratory investigation includes the lipid profile, insulin levels, fasting glucose, and liver and kidney function. The main drugs associated with AN are systemic corticosteroids, oral contraceptives, nicotinic acid, niacin, estrogen, and fusidic acid.¹¹



Figure 20.2 AN in the axillae of an obese patient.

In the syndromic form, AN can be associated with diabetes and autoimmune diseases. When suspicion of associated malignancies exists, it is important to investigate with imaging tests.¹¹

Confluent and reticulated papillomatosis

Confluent and reticulated papillomatosis of Gougerot and Carteau (CRP) is a dermatosis of unknown etiology composed of confluent papules in the central area and reticulated papules in the periphery. It typically occurs on the trunk and neck, although some articles describe atypical forms affecting flexural areas.¹²

In 2006, Davis et al. proposed five diagnostic criteria for CRP: (1) clinical findings of brown scaly macules and plaques with reticulated and papillomatous appearance, (2) involvement of the upper trunk and neck, (3) negative fungal staining of scales, (4) no response to antifungal treatment, and (5) excellent response to minocycline treatment. These criteria are important in the clinical examination, as CRP can mimic other dermatoses, such as AN, seborrheic dermatitis, flat warts, epidermal nevi, tinea versicolor, and cutaneous amyloidosis.¹³

Postinflammatory hyperpigmentation

PIH is an important sequel of inflammatory dermatosis.¹⁴ PIH pathogenesis is not completely understood, but it is known that PIH results from marked production of melanin or from irregular melanin deposit after dispersion by inflammatory mediators.^{14,15} PIH intensity is higher

following chronic inflammatory skin diseases, situations where the basal layer is damaged.¹⁶

Epidermal PIH presents with brownish coloration and, if left untreated, tends to resolve spontaneously in months to years.¹⁵ Histopathological examination shows increased melanin production and transfer to keratinocytes. Dermal PIH has a bluish-gray color and results from melanin deposits in the upper dermis after basal layer damage.

CONCLUSION

The diagnosis of diseases with hyperpigmentation requires a detailed clinical examination, accompanied by a complete medical history and, sometimes, use of auxiliary methods. The dermatologist must be aware of the differential diagnoses discussed in this chapter and must have the ability to use the available auxiliary methods.

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Wood's lamp

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INTRODUCTION

With a clinically well-trained eye and accurate patient history, most skin lesions can be diagnosed with simple visual inspection.

Wood's lamp was invented in 1903 by Robert W. Wood (1868–1955), an American physicist.¹ Its first use in dermatology was described by Margarot and Deveze in 1925 for the detection of hair fungal infection.² Since then, it became a valuable tool for the dermatologist, assisting in the clinical examination and in the differential diagnosis of many diseases. Its possible uses, however, are wider than most physicians know (Table 21.1).

MECHANISM OF ACTION

Wood's light (WL) is a source of ultraviolet (UV) light generated by a high-pressure mercury arc fitted with a compounded filter made of barium silicate with nickel oxide (Wood's filter).^{3,4} This filter is opaque to all wavelengths except for a band between 320 and 400 nm with a peak at 365 nm.^{4,5}

A photon hitting the skin can be reflected away from the skin, scattered deeper into the skin, or absorbed by a molecule. The skin contains a plethora of fluorescent compounds, such as collagen, elastin, coenzymes, and especially melanin, which respond notably to UV light.⁶

The light source should ideally warm up for about 1 minute, and the exam should be conducted in a darkened room. It is important to remember that the eye needs time to adjust to the low-light room in order to see the contrast clearly.^{3,4,6}

DISORDERS OF PIGMENTATION

Melanin absorbs light emitted by WL, so a lesion with an increased concentration of melanin in the epidermis appears darker than the surrounding normal skin. The same does not occur with an increased concentration of melanin in the dermis,³ because the quantity of UV radiation penetrating the dermis is minimal.⁷ On the other hand, in the absence of melanin, the UV radiation is not absorbed but is reflected. Depigmented areas appear bright white under WL due to the autofluorescence of keratin and collagen components of the epidermis and dermis mainly.^{5,8} Thus, both autofluorescence and reflectance contribute to the bright white appearance of non-melanized skin when exposed to WL.⁵

Hypocromic and acromic disorders

WL can help locate and delineate vitiligo patches, especially in fair-skinned individuals, when lesions may be less obvious.⁴ Lesions appear in a bright bluish-white color with sharp demarcations. The UV exam allows us to

distinguish vitiligo from other dermatoses, such as anemic nevus, pityriasis versicolor, and pityriasis alba. Anemic nevus, caused by local dermal vasoconstriction with normal overlying epidermal pigment, and pityriasis alba, with irregular parakeratosis and little melanocyte activity, do not show up in WL.^{3,6} It is also useful for monitoring the repigmentation of vitiligo, because follicular repigmentation after phototherapy can be demonstrated earlier by the use of WL.⁴

The skin findings of hypomelanosis of Ito, especially in lightly pigmented individuals, are not easily visualized in regular light but can be readily seen with the use of WL, which can provide an early diagnosis.^{4,9} The same early diagnosis can be provided in tuberous sclerosis. The first skin finding in these patients is the ash leaf-shaped or lance-ovate hypopigmented macules larger than 10 mm, which are usually present at birth or within the first few months of life.^{4,6,10}

The use of WL also helps in the detection of chemically induced leukoderma and leukoderma associated with melanoma.

Hyperchromic disorders

In melasma, WL exam is useful to confirm the diagnosis and to distinguish whether the pigmentation is predominantly epidermal or dermal. Additionally, the use of WL in melasma has a prognostic value, since epidermal melasma tends to respond more favorably to topical agents.⁴

WL has already been used to determine the borders of lentigo maligna.^{5,11} Because of its ability to accentuate the different pigmentations of skin, it becomes a valuable tool in the preoperative evaluation of hypomelanotic tumors or those situated in extensive photodamaged regions.¹² It can also be used for surveillance of scars after the excision of pigmented lesions, including the follow-up of lentigo maligna excision scars, since pigmentation recurrence can be difficult to recognize under visible light.^{5,13}

PORPHYRIAS

Porphyrias are metabolic disorders caused by a deficiency of one of the enzymes involved in the synthesis of heme. Sensitivity to light occurs due to an excess of porphyrin metabolites.⁶ Porphyrin fluoresces in a pink-orange hue upon WL, and depending on the porphyria, fluorescence can be detected on urine, feces, blood, and teeth (Table 21.1).

SKIN INFECTIONS

There are some bacteria and fungi that produce fluorescent compounds that can be identified with WL, enabling an early diagnosis of some disorders.

Table 21.1 Characteristic fluorescence on main uses of Wood's light exam.

Pigmentary disorders	Color of fluorescence	
Vitiligo	Blue-white	
Tuberous sclerosis		
Hypopigmented mycosis fungoides		
Lentigo	Enhances darkness	
Freckles		
Melasma	Enhances darkness (when epidermal)	
Skin infections		
<i>Microspora</i> sp.	Blue-green	
<i>Trichophyton schoenleinii</i>	Bluish-white	
Pityriasis versicolor	Yellow-white/copper-orange	
Pityrosporum folliculitis	Bluish-white follicular	
Erythrasma (<i>Corynebacterium minutissimum</i>)	Coral-red	
<i>Propionibacterium acnes</i>	Orange-red (comedones)	
<i>Pseudomonas</i>	Yellowish-green	
Porphyrias	Color of fluorescence	Fluorescent source
Erythropoietic porphyria	Red-pink	Urine, teeth, red blood cells
Erythropoietic protoporphyria	Red-pink	Feces, red blood cells
Hepatoerythropoietic porphyria	Red-pink	Feces, urine, red blood cells
Porphyria cutanea tarda	Red-pink	Feces, urine
Variegate porphyria	Red-pink	Feces, urine

Fungi

Tinea capitis can be confirmed using WL when it is caused by *Microspora* species. The hair and scales produce a bright green fluorescence, due to pteridine, a metabolite produced by the *Microspora* species.^{3,6} Diagnosis, however, could not be excluded only by WL examination. *Trichophyton* species do not fluoresce, and even *Microsporum* fungi do not always fluoresce. On the other hand, favus, the most severe form of dermatophyte hair infection, caused by *Trichophyton schoenleinii*, fluoresces bluish-white under WL.

The infected areas of pityriasis versicolor fluoresce yellow-white to copper-orange. Under WL, the infection is often found to be more extensive than what is seen by visual examination.³ It is also useful in diagnosing *Pityrosporum* folliculitis, which appears as a bluish-white fluorescence in the follicular areas, allowing a clear distinction between *pityrosporum* folliculites and a bacterial folliculitis.⁶

Bacteria

Pseudomonas bacteria excrete pyoverdine, a pigment that emits a yellowish-green fluorescence under WL. It can

be used to identify *Pseudomonas* infections or burns or other wounds, long before they show up in bacterial culture.⁶ The exam is also useful for other forms of cutaneous *Pseudomonas* infections, including folliculitis, which tends to occur after immersion in swimming pools or hot tubs, and even for toe web infection.^{4,14}

Erythrasma is caused by *Corynebacterium minutissimum* that grows within the stratum corneum and primarily affects the inguinal, axillary, and submammary folds. Lesions are light coffee color plaques, but can be light red before turning brown. The interdigital spaces of the feet can also be affected, usually with maceration and scaling.¹⁵ Examination with WL shows a bright coral-red fluorescence, as a result of porphyrin produced by the bacteria.^{6,16} For optimal results, affected areas should not be cleaned prior to examination.¹⁵ WL is a direct diagnostic tool that permits us to distinguish erythrasma from intertrigo, tinea, or psoriasis inversa.^{6,16}

Propionibacterium acnes, which is part of the bacterial flora of the skin, produces coproporphyrin III and protoporphyrin IX.⁶ On the facial skin, WL highlights an orange-red fluorescence on comedones, which correlates well with the *P. acnes* population.^{17,18}

OTHER USES

Based on the fact that delta-aminolevulinic acid (ALA)-derived porphyrins accumulate in neoplastic tissues, the use of ALA has been used to diagnose premalignant and malignant conditions. It also helps in the distinguishing of tumor from healthy tissue and benign lesions.¹⁹ ALA ointment (20%) was applied to the tumor and left on for 4–6 hours under occlusion, allowing protoporphyrinogen IX (PpIX) to accumulate; after the time interval, the area is illuminated with WL,²⁰ showing a PpIX area in intense orange-red, which strongly contrasts with the green fluorescence of the normal biological tissues.¹⁹ WL has been proven to be very useful in the diagnosis of basal cell epithelioma, squamous cell epithelioma, Bowen's disease, solar keratosis, and extramammary Paget's disease.^{17,20} Additionally, it also provided a better delineation of the lesion margins.¹⁹

WL exam can also be used to monitor the compliance of patients to treatment with some drugs, such as tetracycline and quinacrine, by the nail exam that shows yellow-green fluorescence.^{4,21} WL has been used in the evaluation of sexual assault victims, because semen on the skin fluoresces, helping to locate areas where semen might have been present, although it is not a very sensitive screening tool.²²

Dermatologists should be aware of false-positive cases, because other products, such as highlighters, dry soaps, laundry detergents, and lemon juice, can fluoresce under WL, mimicking true lesions.²³

CONCLUSION

WL is an inexpensive and very useful tool in the dermatologist's routine. Knowledge of its applications can simplify daily clinical practice.

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MELANOTIC MACULES

The term *melanotic macules* summarizes all skin lesions caused by hyperpigmentation of the basal keratinocytes (pigmented keratinocytes) and a minimal increase of melanocytes in histology. This group includes all types of lentigines of the genital and oral mucosa, lips, and solar lentigines, as well as reticulated black solar lentigo, also known as ink-spot lentigo.¹

Solar lentigo

Solar lentigines typically develop on sun-damaged skin (e.g., face, upper back, and back of the hands) in older individuals appearing as multiple, flat, oval to round, partially bizarrely configured, sharply demarcated, light to dark brown lesions clinically.²⁻⁷ In dermoscopy, these lesions show either a homogeneous brown pigmentation or reticulated and curved thin lines (“fingerprint-like structures”). Additionally, a special dermoscopic criterion of solar lentigines is a sharply demarcated “moth-eaten-like” border (Figure 22.1a and b).²⁻⁷

However, the exact differentiation of pigmented lesion in sun-exposed regions may be challenging because of some overlapping features clinically, as well as in dermoscopy. The differential diagnoses include early seborrheic keratosis, pigmented actinic keratosis, lichen planus-like keratosis, and lentigo maligna.²⁻⁷

Typical dermoscopic clues of lentigo maligna helpful in the differentiation from solar lentigo are asymmetrically pigmented follicles, an annular-granular pattern, a circle within the circle, and a gray pseudonetwork. Gray color is supposed to be the single most sensitive feature indicating lentigo maligna.²⁻⁷

Ink-spot lentigo

Ink-spot lentigines commonly appear in fair-skinned individuals on sun-exposed skin as a single, darkly pigmented, sharply demarcated macule with peripheral fingerlike extensions. In contrast to common solar lentigines, the ink-spot lentigo usually arises as a single lesion among several solar lentigines.⁸⁻¹⁰

Ink-spot lentigines typically show a reticulated pattern in dermoscopy with dark brown or black “broken-up” lines. The width of the lines may vary within one lesion, however. A special dermoscopic criterion of ink-spot lentigines is sporadically disrupted lines, which end precisely on the lesion’s margin (Figure 22.2a and b).⁸⁻¹¹

Labial melanotic macule

A labial melanotic macule usually arises after sun exposure as a single, well-defined, brown or black-brown

macule, 2–10 mm in diameter, on the vermillion border of the lower lip, mostly in adult women with a mean age of 30 years.¹²⁻¹⁵

A diffuse, brown or black, homogeneous pigmentation gradually fading toward the periphery is the most common dermoscopic feature of labial melanotic macules.^{6,11-13} Another characteristic dermoscopic sign concerning labial melanotic macules is a parallel pattern, characterized by linear or partially curved pigmentary lines arranged regularly in a parallel manner (Figure 22.3a and b).^{12,16}

Mucosal melanotic macule

Mucosal melanotic macules mostly appear as a single, brown to black, well-defined, asymptomatic macule, 0.5–2 cm in size, that may clinically mimic melanoma.¹⁷⁻²⁷ The most frequent locations of these macules are the labia minora, glans penis, gingiva, palate, and buccal mucosa.^{17,19} The mean age of onset of the mucosal manifestation is approximately 40 years.^{17,19,21} Dermoscopically, the lesions commonly exhibit a homogeneous brown or black pigmentation (Figure 22.4a and b).^{17,18,22-25,27-30} The parallel pattern is a very prominent dermoscopic feature seen in genital melanosis as well. In literature, a fingerprint pattern with narrow parallel lines and broader track-like pigmentation interrupted by brown or black dots and globules is described as the most common dermatoscopic feature in mucosal melanotic macules.^{17,22-27,29,30} Ferrari et al.²⁶ first described a ringlike pattern dermoscopically, characterized by multiple round to oval structures, to be only present in genital melanosis. Therefore, this pattern may represent a new clue to recognize these lesions and differentiate them from melanoma.

On the other hand, blue, gray, or white structureless areas within the lesion, as well as irregular dots in dermoscopy, are very strong indicators for malignancy, and histopathological examination is required. In several studies, blue color indicated melanoma in up to 75% of the cases, and gray color in up to 72.7%.^{17,18,22-27,29-31}

CUTANEOUS MASTOCYTOSIS

Cutaneous mastocytosis is a skin disease characterized by a proliferation and accumulation of mast cells in the skin. It is classified into three clinical subtypes: maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis, and solitary mastocytoma. In addition, the maculopapular type is divided into three entities: papular or plaque variant, urticaria pigmentosa, and eruptive macular teleangiectasia perstans.³²⁻⁴⁰

Urticaria pigmentosa is the most common form of cutaneous mastocytosis.

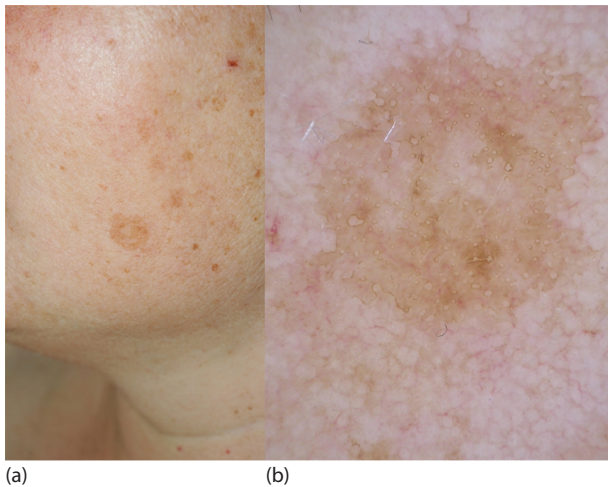


Figure 22.1 (a and b) Clinical and dermoscopic image of solar lentigo showing a sharply demarcated “moth-eaten-like” border.

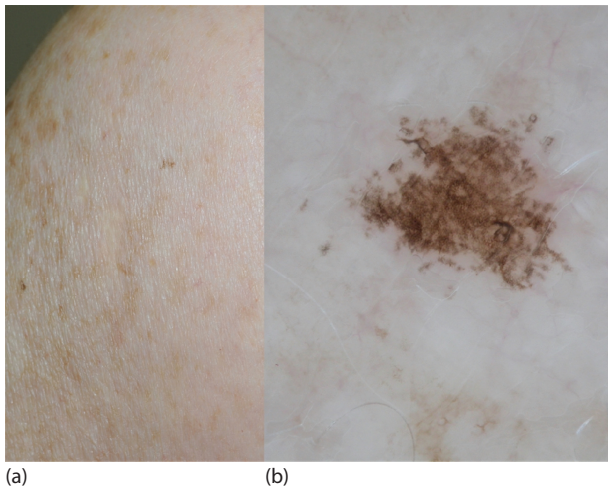


Figure 22.2 (a and b) Clinical and dermoscopic image of ink-spot lentigo. Dermoscopy shows dark brown “broken-up” lines, which end precisely on the lesion’s margin.

It is characterized clinically by monomorphic, symmetrically arranged, brownish macules, papules, plaques, or nodules, mainly on the trunk.^{32–40}

Four different dermoscopic patterns can be observed in cutaneous mastocytosis: a yellow-orange blot, a pigment network, a reticular vascular pattern, and most frequently, a light brown blot. A pigment network, as well as a light brown blot, is usually seen in urticaria pigmentosa (Figure 22.5a and b).^{32,34,36–38}

It is believed that the pigment network seen with dermoscopy is due to a high concentration of mast cell growth factor stimulating melanocyte proliferation and melanogenesis, thus leading to hyperpigmentation of basal keratinocytes.^{32,35–38}

A pigment network is not exclusively found in melanocytic lesions by dermoscopy. There are a few studies

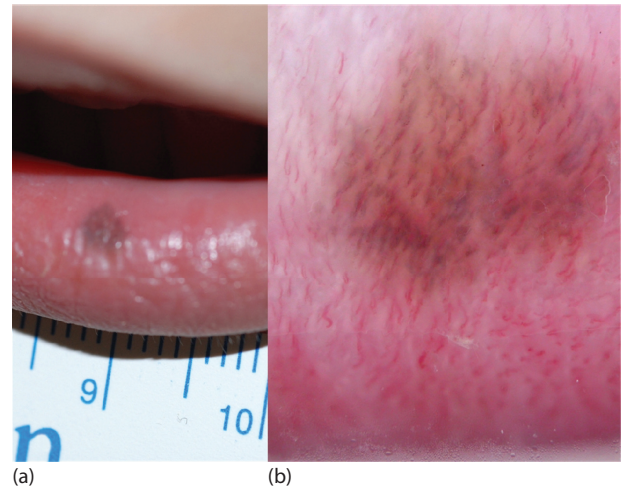


Figure 22.3 (a and b) Clinical and dermoscopic image of labial melanotic macule with brown linear lines arranged regularly in a parallel manner dermoscopically.

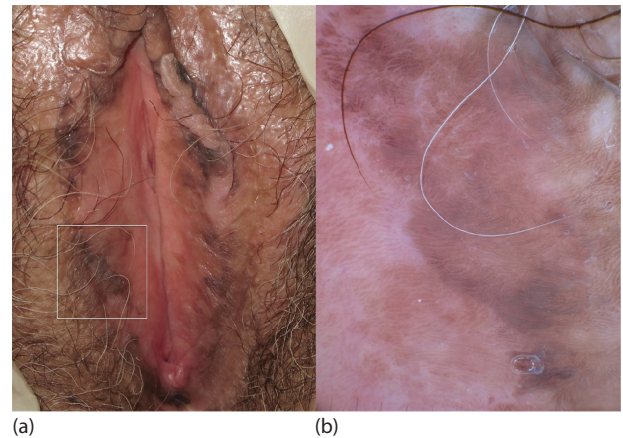


Figure 22.4 (a and b) Clinical and dermoscopic image of genital melanosis showing diffuse gray-brown pigmentation composed of parallel lines.

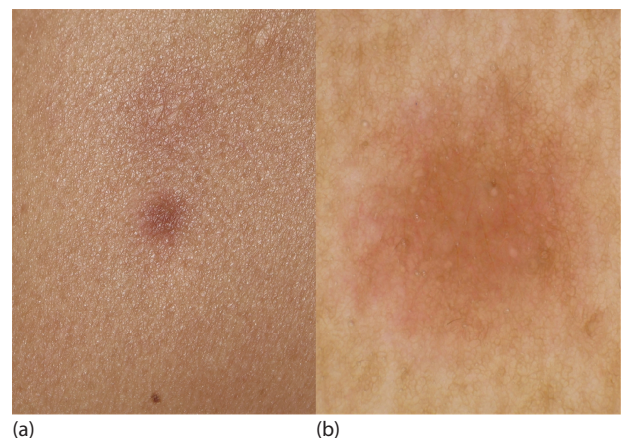


Figure 22.5 (a and b) Clinical and dermoscopic image of cutaneous mastocytoma. Dermoscopy reveals a central light brown to orange pigmentation and a delicate pigment network.

describing a pigment network present in other lesions, like seborrheic keratoses and dermatofibroma. The reticular vascular pattern, consisting of thin reticular telangiectasias, is a typical dermoscopic feature in eruptive macular telangiectasia perstans, and therefore is helpful in differentiating this kind of cutaneous mastocytosis from other variants. There is agreement that a yellow-orange blot pattern is present in all solitary mastocytomas. Conclusively, dermoscopy may facilitate the differentiation of cutaneous mastocytoses and set them apart from other exanthematous skin diseases.^{32–40}

PRIMARY CUTANEOUS AMYLOIDOSIS

Amyloidosis is a large and heterogeneous group of disorders characterized by extracellular deposits of amyloid in individual organs or tissue. It is either hereditary or acquired. Primary cutaneous amyloidosis is a very rare disease, and therefore just a few cases have been described so far.^{41–44}

Lichen amyloidosis is the most common subtype of cutaneous amyloidosis. Skin-colored to gray-brownish papules that cause intense itching, located mainly on the trunk and extremities, are typical clinical findings.^{41–44}

Until now, there is only one study describing dermoscopic features in primary cutaneous amyloidosis.⁴⁴ This group exhibited two dermoscopic patterns seen in this skin disorder. In macular amyloidosis, they reported a central hub, either white or brown, surrounded by various configurations of pigmentation. In lichen amyloidosis with prominent hyperkeratosis, the central hub was replaced by a scar-like morphology.

REGRESSING LICHEN RUBER PLANUS: ASHY DERMATOSIS

Ashy dermatosis is a rare, acquired skin disorder associated with diffuse gray-brownish discoloration, especially on the trunk, the neck, and the upper extremity. Its etiology is unknown. A postinflammatory hyperpigmentation through drug intolerance, viral infections (hepatitis B), endocrinological and immunological phenomena, and a relation to lichen ruber are presently discussed as causal factors.^{45–47}

In the case of a relation to lichen planus, dermoscopy reveals regressing gray macules with granular gray-brown dots and globules (dermal melanophages) on a yellow-brownish background (Figure 22.6a and b). A large amount of granules seems to indicate a slower course of disappearance of the dyschromatic macules. Additionally, the dots and globules outline Wickham striae or are clustered in the depressed centers of some Wickham striae.^{45–47}

MELASMA

Melasma is an acquired hypermelanosis of the skin with a chronic course that occurs symmetrically on sun-exposed areas, especially on the face and cervical region, predominantly in women. The exact causes are unknown; however, some triggering factors have been described: genetic

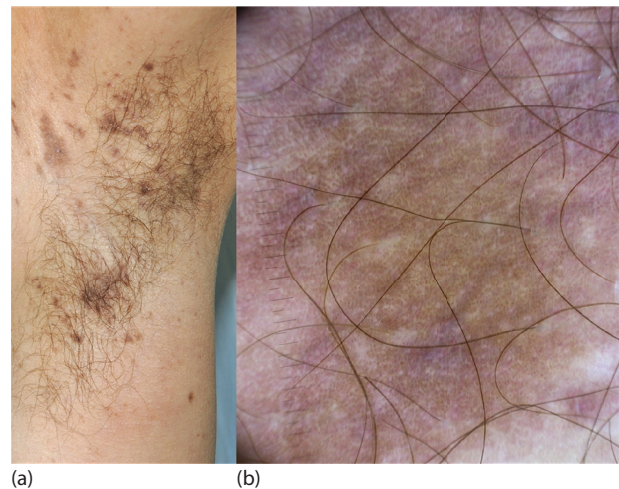


Figure 22.6 (a and b) Clinical and dermoscopic image of regressing lichen ruber planus showing granular gray-brown dots and globules on a yellow-brownish background.

predisposition, ultraviolet (UV) radiation exposure, hormonal factors such as female sex hormones and thyroid disease, pregnancy, and drugs like phenytoin are known risk factors.^{48–52}

Melasma is characterized by brownish macules with irregular, but well-defined margins clinically.^{48–52}

Dermoscopy of melasma shows a diffuse reticular pigmentation in various shades of brown and more intense telangiectasies compared with normal skin. The color intensity and the regularity of the pigment network reveal the density and location of melanin. Lesions present as dark brown in color and with a well-defined network when melanin is located in the stratum corneum. Shades of light brown and irregularity of the network are observed when melanin is located in the lower layers of the epidermis. Melanin located in the dermis corresponds to blue or bluish-gray color.^{48,49}

PIGMENTATION WITHIN A SCAR

Melanotic pigmentation within a scar consecutive to the excision of melanocytic lesions can be due to either a reactive phenomenon related to the scar tissue or a recurrence of the excised melanocytic lesion.^{53–57} There are four dermoscopic features allowing a differentiation between reactive and melanocytic pigmentation in a scar. The presence of globules and a heterogeneous pigmentation is highly correlated with a specific melanocytic pigmentation. On the other hand, a regular network, as well as streaks, is a strong indicator of reactive pigmentation (Figure 22.7a and b).^{53,54} In recurrent nevi radial lines, symmetry and a centrifugal growth pattern are typical dermoscopic findings. On the contrary, circles, especially in the head and neck region, an eccentric hyperpigmentation at the periphery, and a chaotic and noncontinuous growth pattern are indicative of a recurrent melanoma. However, pigmentation beyond the scar's edge is the strongest clue for melanoma.^{53–57}

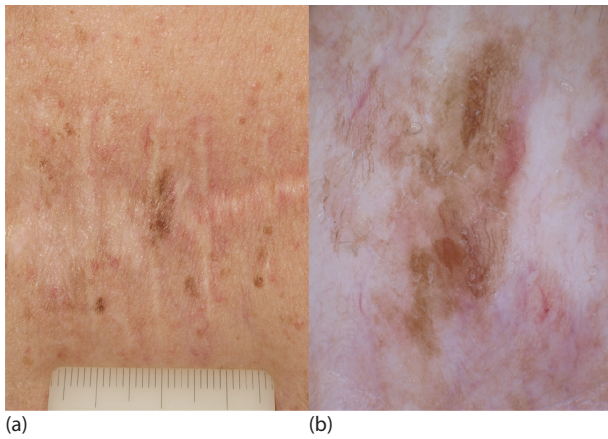


Figure 22.7 (a and b) Hyperpigmentation arising within the scar after surgical excision of an invasive melanoma. Dermoscopy shows brown-colored parallel lines and light brown structureless pigmentation.

TINEA NIGRA

Tinea nigra is an asymptomatic superficial pheohyphomycosis caused by the mold *Hortaea werneckii*, which mainly occurs in tropical or subtropical regions. *Phaeoannellomyces werneckii* is a saprobic fungus living in environments like soil, plants, beach, sand, air, and decomposing fish. This mycosis usually affects children and adolescents, particularly girls.^{58–64} Clinical examination reveals well-defined, nondesquamative, irregularly pigmented, gradually enlarging macules and patches exclusively on the skin of the palms and soles. Superficial thin, wispy, brown pigmented spicules not respecting the dermatoglyphic lines are typical findings in dermoscopy (Figure 22.8a and b). Therefore, dermoscopy can also aid in distinguishing this mycosis from melanocytic lesions of the palms and soles.^{58–64}

ONYCHOMYCOSIS

In the most common form of clinical onychomycosis, the first and/or fifth toenail is typically affected by a

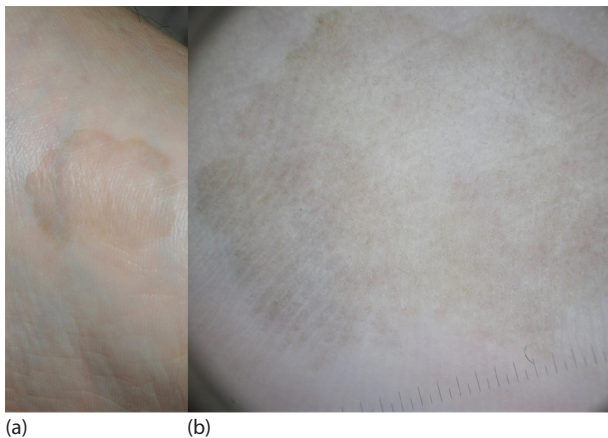


Figure 22.8 (a and b) Clinical and dermoscopic image of tinea nigra revealing thin, light brown, pigmented spicules.

distolateral pattern. A range of dermoscopic features are described to be present in onychomycosis: whitish discoloration of the nail with superimposed longitudinal parallel striation and jagged proximal edges (Figure 22.9a and b). Additionally, small splinter hemorrhages and various nail discolorations (chromonychia) with green, yellow, or brown color may be observed. Moreover, an intense green color of the nail plate affected by a mycotic infection may indicate a secondary infection with *Pseudomonas* species (Figure 22.10a and b).^{65–70}

NEVOID LENTIGO OF THE NAIL UNIT

This lentigo of the nail unit predominantly occurs in humans with a darker skin type according to Fitzpatrick's skin classification (skin type V). Usually, multiple nails are

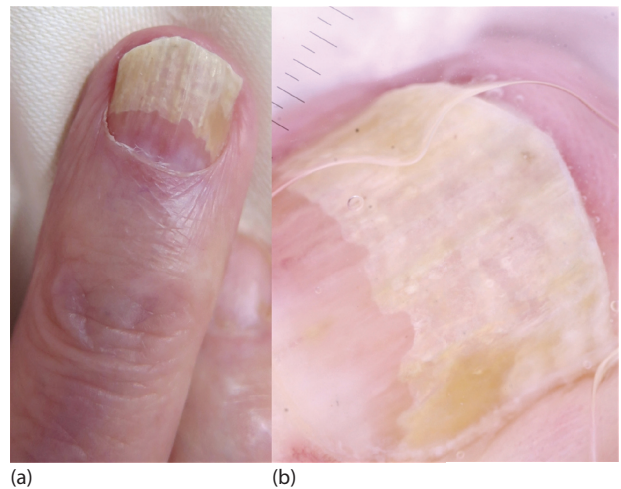


Figure 22.9 (a and b) Clinical and dermoscopic image of onychomycosis showing a whitish discoloration of the nail with jagged proximal edges.

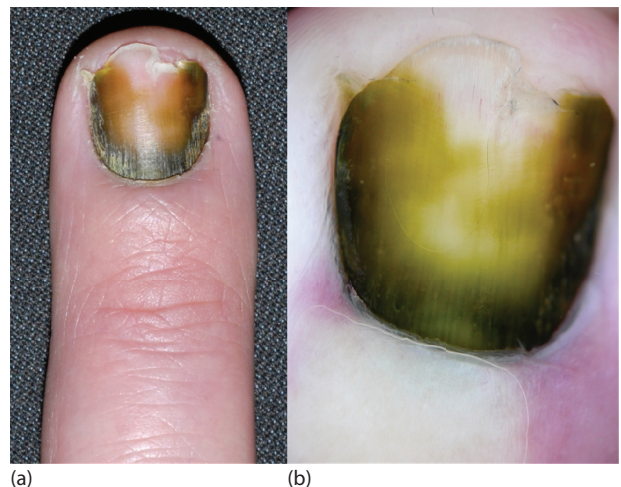


Figure 22.10 (a and b) Clinical and dermoscopic image of secondary infection with *Pseudomonas* species with intense green coloration of the nail plate.

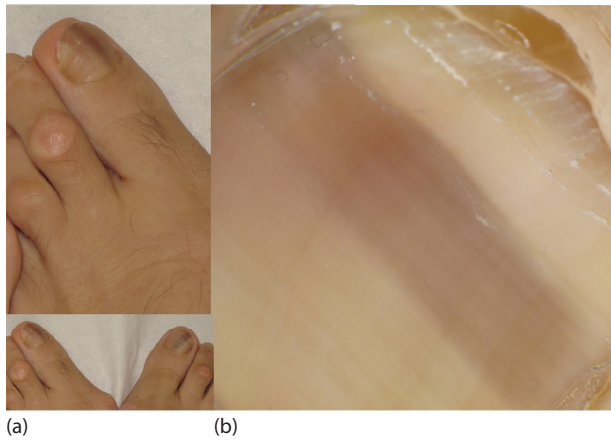


Figure 22.11 (a and b) Clinical and dermoscopic image showing melanonychia of the toe. Note the involvement of more than one nail (inset). Dermoscopy reveals a uniform gray band-like pigmentation.

affected and the lesions are homogeneous gray-brown colored clinically.

Homogeneous, longitudinal, thin gray lines, regular in coloration, thickness, and spacing, on a grayish background, are typical dermoscopic findings (Figure 22.11a and b). The lateral margin of the pigmentation is often diffuse. Occasionally, the pigmented band is very subtle and pale and differentiating it from the uninvolved nail plate may be difficult.^{65–67,70}

LAUGIER–HUNZIKER SYNDROME

This syndrome is defined as a rare, acquired, benign, macular hyperpigmentation of the lips and oral mucosa associated with longitudinal melanonychia. Its etiology is still unknown, and it seems that neither familiar predisposition nor systemic or malignant disease is associated with the syndrome.^{71–74}

It is characterized by asymptomatic, light to dark brown, partly diffuse, distributed macules of the oral mucosa and homogenous band-like hyperpigmentation of the nails clinically. In mucosal lesions, a brownish reticular parallel pattern can be observed dermoscopically. The nails show homogenous, brownish and grayish longitudinal bands and lines with ill-defined margins. A pseudo-Hutchinson's sign can also be observed in these lesions.^{71–74}

SUBUNGUAL HEMORRHAGE AND SUBUNGUAL HEMATOMA

The subungual hemorrhage is one of the most frequent differential diagnoses concerning acral pigmented lesions. Clinical examination usually reveals a reddish-blue to blue-black pigmentation not involving the whole nail. A homogeneous or globular pattern, streaks, peripheral fading, and hemorrhage of adjacent skin are typical patterns found in dermoscopy. Moreover, small, globular blood dots toward the distal end of the nail plate are a highly characteristic feature dermoscopically (Figure 22.12a and b).

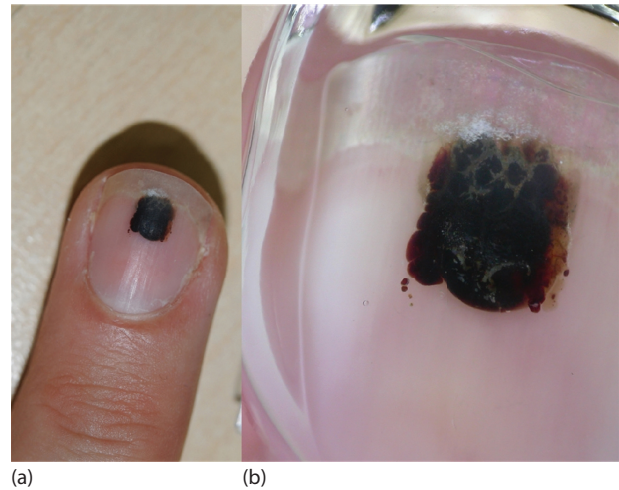


Figure 22.12 (a and b) Clinical and dermoscopic picture of subungual hemorrhage. Dermoscopy shows a homogeneous reddish pattern with small blood dots toward the distal end of the nail plate.

Importantly, a proximal subungual hematoma may be visible through the widely transparent cuticula and has to be distinguished from the micro-Hutchinson sign, indicating subungual melanoma.^{65–67,75}

DRUG-INDUCED NAIL PIGMENTATION

A range of drugs have been associated with pigmentation of the nails. However, only a few drugs are responsible for toxic effects on the nail matrix, the nail bed, or the periungual skin. This group predominantly includes retinoids and chemotherapeutics like docetaxel. After treatment with docetaxel, diffuse dark pigmentation of all nails, Beau's lines (horizontal and deep grooves of all fingernails), or yellow-reddish discoloration (increased vascularization of the nail matrix) can be observed. It has to be considered that this type of nail alteration is related to the number of administered cycles.

The presence of thin, longitudinal blue-gray lines, regular in thickness, spacing, and coloration, on a grayish background, is a typical dermoscopic finding after prolonged minocycline treatment.^{65–67}

EXOGENOUS BLUE PIGMENTATION

Any kind of exogenous dermal pigmentation, such as an amalgam tattoo or cosmetic tattoo, appears as a blue coloration in dermoscopy (Figure 22.13a and b). A structureless blue pattern can be observed in these lesions dermoscopically.

Amalgam tattoos are common, asymptomatic solitary oral macules or patches with a blue, gray, or black coloration. These lesions usually occur on the gingiva, but are also seen on the buccal and alveolar mucosae, the palate, or the tongue. They are due to a desposition of small particles of amalgam (mixture of silver, mercury, zinc, and copper) into the oral soft tissue. Importantly, amalgam tattoos may be mimicking a blue nevus, mucosal melanoma, or

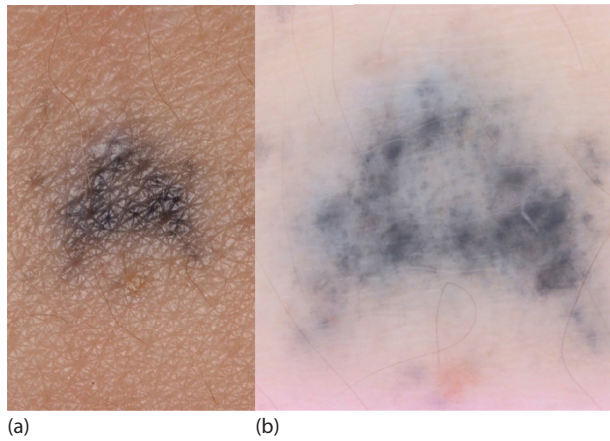


Figure 22.13 (a and b) Clinical and dermoscopic image of self-inflicted tattoo with a structureless blue pattern in dermoscopy.

vascular lesions. In doubtful cases or when a mucosal melanoma cannot be ruled out, a punch biopsy should always be performed. Another clue for the diagnosis might be performing a radiography of the area, as amalgam presents as a highly reflective area in the image.^{76–78}

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INTRODUCTION

This chapter summarizes conditions typified clinically by hyperpigmentation that can be diagnosed by specific histopathologic changes. Some diseases with very similar histopathologies but diverse clinical findings have also been included to demonstrate the limitations of histopathological diagnosis. It has to be taken into account, however, that a number of conditions with hyperpigmentation are extremely rare or rarely biopsied, and therefore experience with histopathologic changes in them is quite limited (e.g., idiopathic eruptive macular pigmentation, universal acquired melanosis, patterned hypermelanosis, and dyschromatosis symmetrica hereditaria [reticulate acropigmentation of Dohi]).¹⁻³

The clinical finding of hyperpigmentation can be caused by a broad variation of histopathological changes. Therefore, a biopsy can be helpful when the cause and mechanism of hyperpigmentation in a patient cannot be identified clinically. The reason for clinically pigmented skin can be found

1. In the cornified layer
2. In the epidermis
3. In the dermis or deeper tissues

In general, pigment under the microscope is much less impressive than clinically. Even dark pigmented melanocytic neoplasms may show only faint pigmentation histologically. Moreover, it has to be considered that epidermal pigmentation in the normal skin varies greatly according to skin type. Therefore, histopathologic diagnosis of pigmentary alterations can be quite challenging and may require comparison with normal skin of the same site and correlation with clinical findings.³

In the following, various disorders of hyperpigmentation are discussed with their histopathological correlates according to the histological level of the pigmentary change.

HYPERPIGMENTATION IN THE CORNIFIED LAYER

Pigmentation in the cornified layer may be caused by exogenous pigment, such as self-tanner or dirt; hyperkeratosis, like in terra firma-forme dermatosis (dermatosis neglecta); pigmented organisms in the cornified layer, as is the case in tinea nigra and pityriasis versicolor; or cornification of pigmented keratinocytes, as is often seen above heavily pigmented benign and malignant melanocytic neoplasms.

Self-tanning products

Self-tanners contain sugar molecules like dihydroxyacetone or erythrulose that react with proteins and amino acids of the cornified layer, leading to discoloration.⁴ The

pigmentation can be seen as brownish discoloration of the uppermost corneocytes and in the form of pigmented droplets throughout the cornified layer (Figure 23.1).

Terra firma-forme dermatosis (dermatosis neglecta)

The cause of terra firma-forme dermatosis is not entirely known, but the histopathological correlation of clinically grayish pigmentation is simply lamellar hyperkeratosis.⁵

Tinea nigra

Tinea nigra is a superficial mycosis caused by *Phaeoannellomyces (Exophiala) wernecki*. The organism belongs to the group of pigments producing Dematiaceae (black yeast), which also cause other diseases, like chromomycosis and pheohyphomycosis.^{6,7} The clinical presentation of a sharply demarcated pigmented patch in an acral location is caused by the presence of multiple pigmented hyphae and spores in the stratum corneum (Figure 23.2). The pigment is melanin, which is produced by the fungus and deposited in its cell wall.

Pityriasis versicolor

Pityriasis versicolor (or tinea versicolor) is a superficial infection of the skin with *Malassezia globosa* or *Malassezia furfur* (formerly called *Pityrosporum ovale* or *Pityrosporum orbiculare*). The lipophilic yeasts are part of the normal flora of the hair follicle, which may under certain conditions, such as hyperhidrosis, overgrow the epidermal flora.^{7,8} The short and plump hyphae and spores are typically located in the upper parts of the cornified layer ("spaghetti and meatball sign") (Figure 23.3). *Malassezia* can be easily identified as basophilic structures on routine stains with hematoxylin and eosin (in contrast to dermatophytes, which usually require staining with periodic acid-Schiff). Nevertheless, special stains for fungi also help to identify the organisms. Just like *P. wernecki*, *Malassezia* produces melanin, which leads to clinically pigmented skin in pityriasis versicolor. In contrast, hypopigmented lesions develop by photoprotective effects of the fungal elements, which produce dicarboxylic acids that inhibit tyrosinase and thereby melanin synthesis.

Pigmented cornification above melanocytic neoplasms

Melanocytic neoplasms, both benign and malignant, may be covered by a heavily pigmented cornified layer. This is particularly important to know because the intracorneal pigmentation makes dermatoscopic examination of the neoplasm difficult, if not impossible. The pigmentation of the cornified layer is a result of heavy pigmentation of

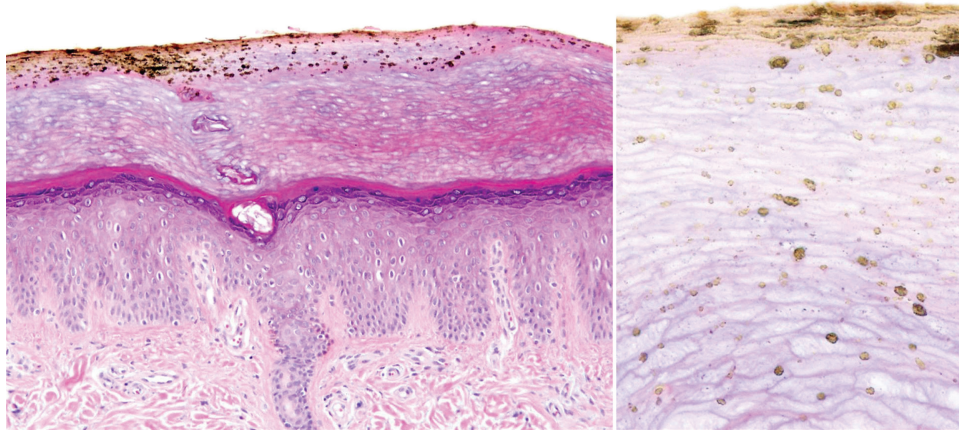


Figure 23.1 Self-tanner. Pigmented droplets in the uppermost corneocytes.

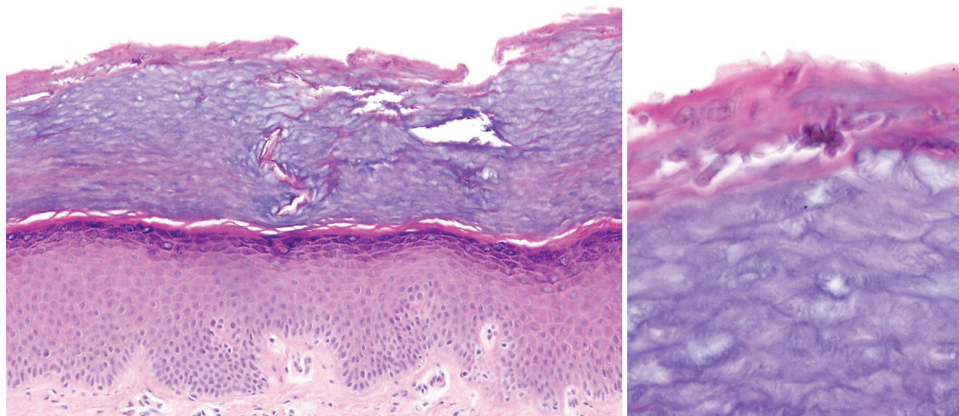


Figure 23.2 Tinea nigra. Pigmented hyphae and spores in the cornified layer.

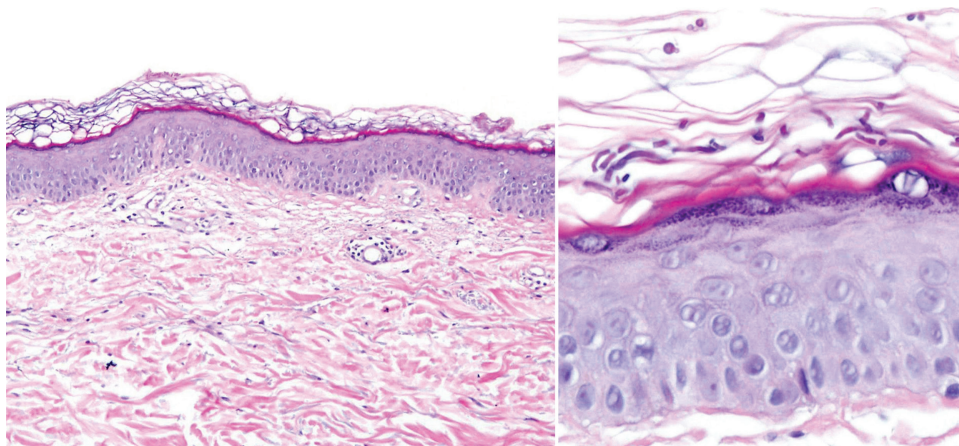


Figure 23.3 Pityriasis versicolor. Plump hyphae and spores in the upper parts of the cornified layer (spaghetti and meatball sign).

epidermal keratinocytes that derive their pigmentation from the melanocytes. If a melanocytic lesion presents with a structureless black zone on dermatoscopy, tape stripping of the lesion should be performed in order to remove a heavily pigmented cornfield layer.⁹ After that, dermatoscopy should be applied again, which will then disclose the pigment network of the neoplasm.

HYPERPIGMENTATION OF THE EPIDERMIS

Various and disparate conditions are typified by hyperpigmentation of the epidermis, and differentiating them mostly requires clinicopathological correlation. Conditions with pigmentation can only be differentiated from those that show pigmentation, as well as acanthosis of the epidermis. In the group of diseases with hyperpigmentation only, melanotic macule of the lip and its analogues, benign melanosis of the vulva and penis, and ink-spot lentigo can be found, as well as café-au-lait macules, and ephelides. Diseases that combine epidermal pigmentation with acanthosis include acanthosis nigricans, Morbus Gougerot-Carteaud (papillomatosis confluens et reticularis), Morbus Dowling-Degos, and Galli-Galli disease, but also solar lentigo, seborrheic keratosis, Becker's nevus, and some epidermal nevi. In addition, epidermal hyperpigmentation

may also be seen consequent to the effects of infiltrates of inflammatory cells, e.g., in late-stage morphea, in mastocytosis, and above dermatofibroma.

Melanotic macule of the lip and benign melanosis of the vulva and penis

In melanotic macule of the lip, just as in benign melanosis of the vulva and penis, no proliferation of melanocytes is seen in the epithelium. Melanocytes are present as single melanocytes and evenly distributed.¹⁰⁻¹² There is hyperpigmentation of the epidermal keratinocytes, which is accentuated in the basal layer and most prominent at the base of rete ridges (Figures 23.4 and 23.5). In the syndrome of Laugier-Hunziker, melanotic macules of the lips and oral mucosa may be associated with melanosis of the genital mucosa and pigmented streaks of the nail unit, all of them showing histologically essentially the same features of increased pigmentation of basal keratinocytes emphasized at the base of rete ridges.

Ink-spot lentigo

Ink-spot lentigo is a clinically distinctive, often reticulated, dark pigmented lesion that is histologically devoid of a proliferation of melanocytes.¹³ Basal keratinocytes

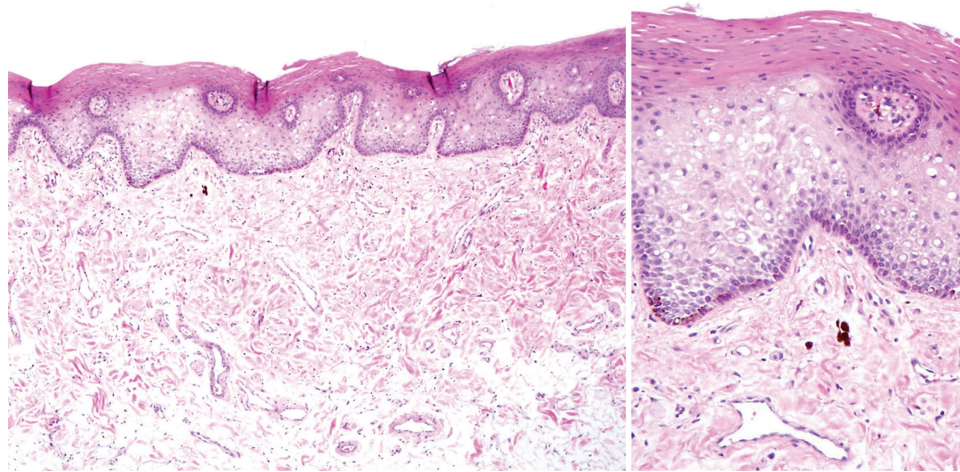


Figure 23.4 Melanotic macule of the lip. Hyperpigmentation of the basal layer, most prominent at the base of rete ridges.

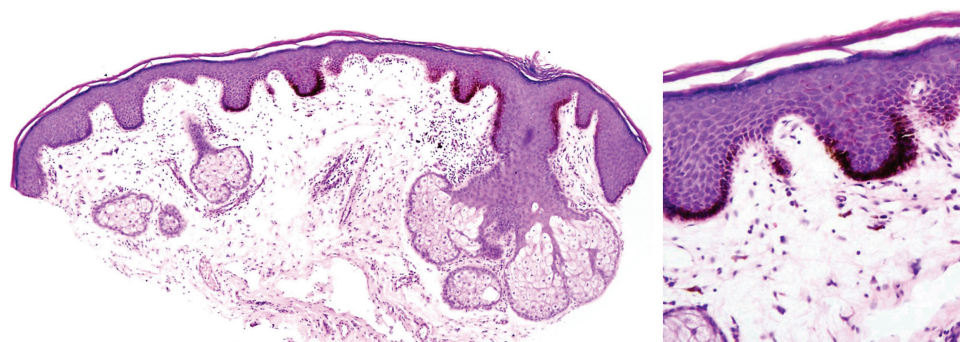


Figure 23.5 Benign melanosis of the genitalia. Hyperpigmentation of the basal layer, most prominent at the base of rete ridges.

are hyperpigmented most prominently at the base of rete ridges, similar to the situation in melanotic macule and its analogues.

Café-au-lait macule

The pigmented patches of café-au-lait spots are histopathologically typified by an increased pigmentation of basal keratinocytes (Figure 23.6).¹⁴ Melanocytes may be slightly increased in number, but no nests of melanocytes are seen. Sometimes, melanocytes contain macromelanosomes.

Ephelides

Ephelides are small-sized hyperpigmentations on the facial skin, neck, and shoulders, usually in patients with fair skin types.¹⁵ They are hardly ever biopsied because of their typical clinical appearance. Histologically, hyperpigmentation of basal keratinocytes is the only abnormality. The number of melanocytes is normal.

Melasma

Melasma is clinically typified by patchy pigmentation of the face, often connected to pregnancy or hormone

intake.^{1,16,17} Histopathologically, the changes are subtle and consist of slight basal epidermal hyperpigmentation.

Becker's nevus

Becker's nevus presents clinically as a mostly unilateral hyperpigmentation of the upper trunk, usually in male adolescents. Often, the number of terminal hairs in the lesion is increased. Therefore, Becker's nevus can be considered a hamartoma (Figure 23.7).¹⁸ Sometimes, smooth muscles are also increased, giving the appearance of smooth muscle hamartoma. Histologically, increased pigmentation is mainly seen in the basal keratinocytes. No melanocytic proliferation is present. There are also variable epidermal acanthosis and papillomatosis.

Acanthosis nigricans

Acanthosis nigricans presents clinically with hyperkeratotic or even verrucous pigmentation, mainly on the neck and the big flexures. The condition may be associated with a variety of diseases, including adenocarcinomas, endocrine disorders affecting the insulin levels, and drug intake (oral contraceptives, somatotropin, etc.).¹⁹ A biopsy

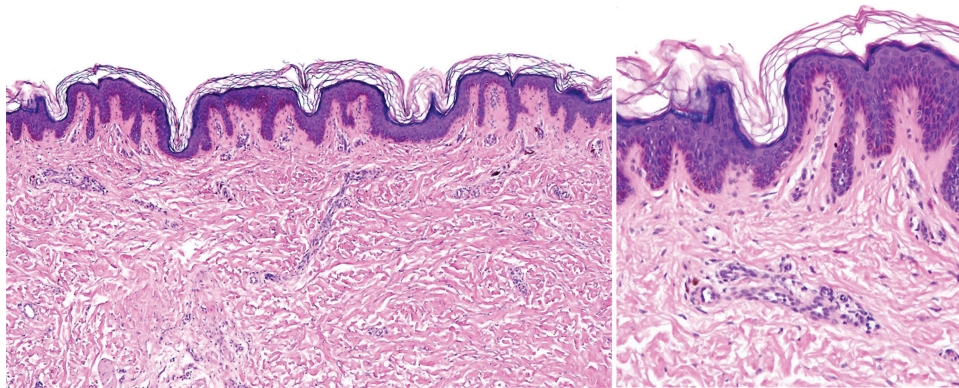


Figure 23.6 Café-au-lait macule. Hyperpigmentation of basal keratinocytes.

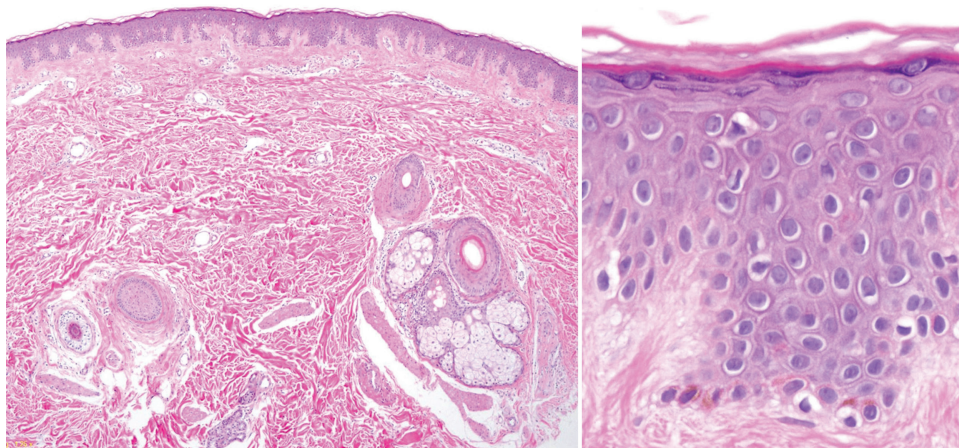


Figure 23.7 Becker's nevus. Hyperpigmentation of basal keratinocytes, together with an increased number of terminal hair follicles.

shows verrucous architecture with mild acanthosis of the epidermis and varying papillomatosis and basal hyperpigmentation (Figure 23.8). The appearance resembles that of seborrheic keratosis, but the valleys between fingerlike projections are relatively deep.

Confluent and reticulate papillomatosis (Gougerot–Carteaud)

Reticulate pigmentation with slightly verrucous appearance is typical of Gougerot–Carteaud disease. Lesions are distributed symmetrically on the upper trunk, usually in young men. The extremities and neck may also be affected.^{20–22} Histopathologically, the changes are similar to those of acanthosis nigricans, but often show a Y-shaped configuration of rete ridges, and acanthosis, as well as papillomatosis, is less prominent (Figure 23.9). The basal layer shows a slight increase in pigmentation. Out of the clinical context, the changes are easily misinterpreted as a seborrheic keratosis.

Dowling–Degos disease

Reticulate pigmentation of the body folds is the typical clinical appearance of Dowling–Degos disease. The condition is inherited in autosomal dominant traits and mutations in the keratin 5 gene, POFUT1 gene, and POGLUT1 gene, and others have been identified to be associated with it.^{23,24} Histopathologically, filiform proliferation of the epidermis associated with hyperpigmentation of the basal keratinocytes at the base of rete ridges is characteristic (Figure 23.10). The appearance is quite similar to that of reticulated seborrheic keratosis.

Galli–Galli disease

Galli–Galli disease may present itself with clinical features indistinguishable from those of Dowling–Degos disease, or with more maculopapular manifestations reminiscent of generalized Grover's disease.^{25,26} On microscopy, the filiform proliferation of the epidermis with basal hyperpigmentation is largely identical to that seen in Dowling–Degos disease, but in addition, suprabasal acantholysis is present (Figure 23.11). The pattern can be quite similar to

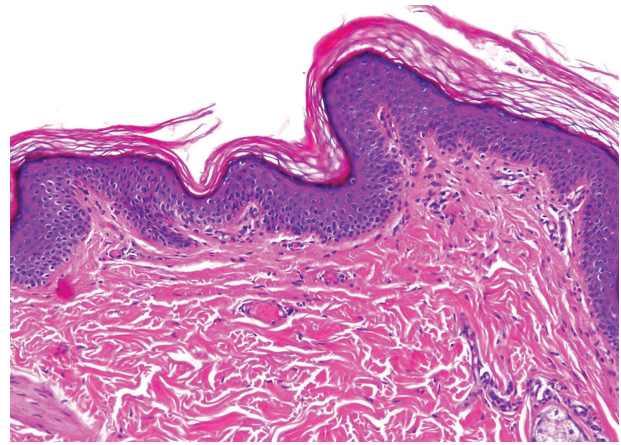


Figure 23.9 Confluent and reticulate papillomatosis (Gougerot–Carteaud). Slight acanthosis, papillomatosis, and basal hyperpigmentation.

that seen in some variants of Grover's disease. The observation that mutations in the keratin 5 gene and POGLUT1 gene have been identified in patients diagnosed with Galli–Galli disease led to the view that it may represent a variant of Dowling–Degos disease, rather than a distinct entity.

Solar lentigo

Solar lentigo is a pigmented macule or patch that occurs on sites of chronic sun exposure. It is often seen in continuity with flat seborrheic keratosis, and therefore is increasingly viewed as a very incipient lesion of seborrheic keratosis. Histopathologically, fingerlike projections of the epidermis are found in a regular arrangement above a sun-damaged dermis (Figure 23.12).^{16,27} The basal layer shows increased pigmentation of keratinocytes, but no proliferation of melanocytes. While melanocytes may be slightly increased in number as a result of chronic sun exposure (so-called actinic hyperplasia of melanocytes), those melanocytes are regularly distributed and do not form nests. Solar lentigo may occur in collision with solar keratosis or

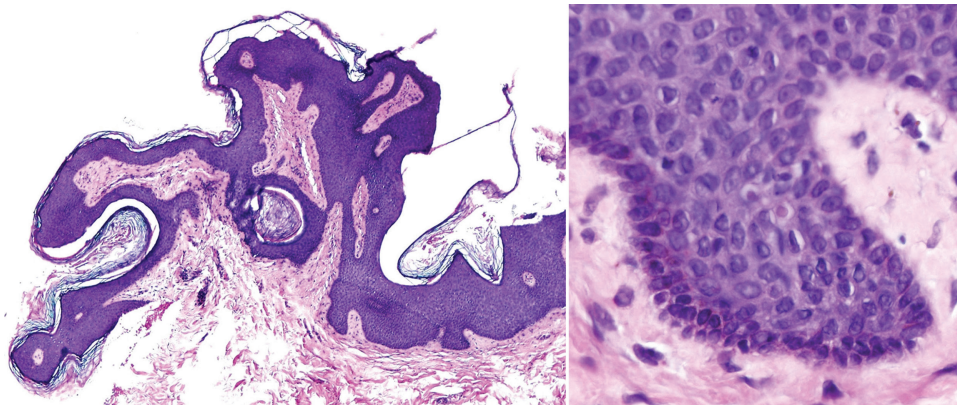


Figure 23.8 Acanthosis nigricans. Acanthosis, papillomatosis, and basal hyperpigmentation.

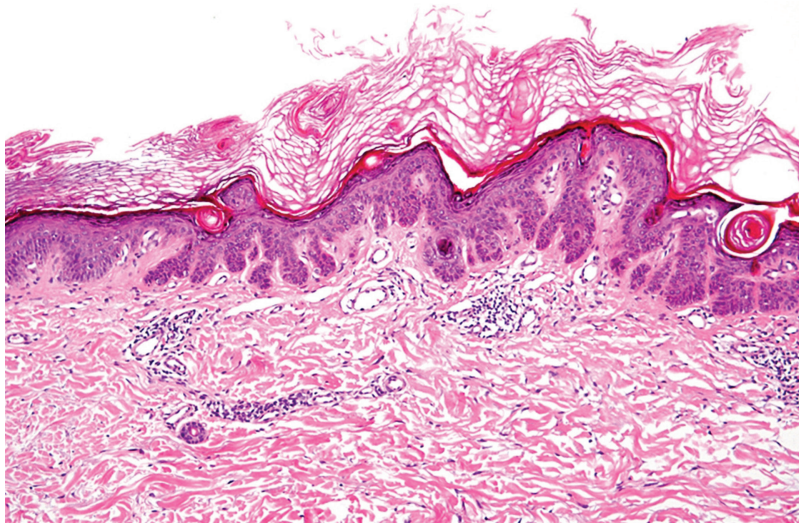


Figure 23.10 Dowling–Degos disease. Filiform proliferation of rete ridges, together with basal hyperpigmentation.

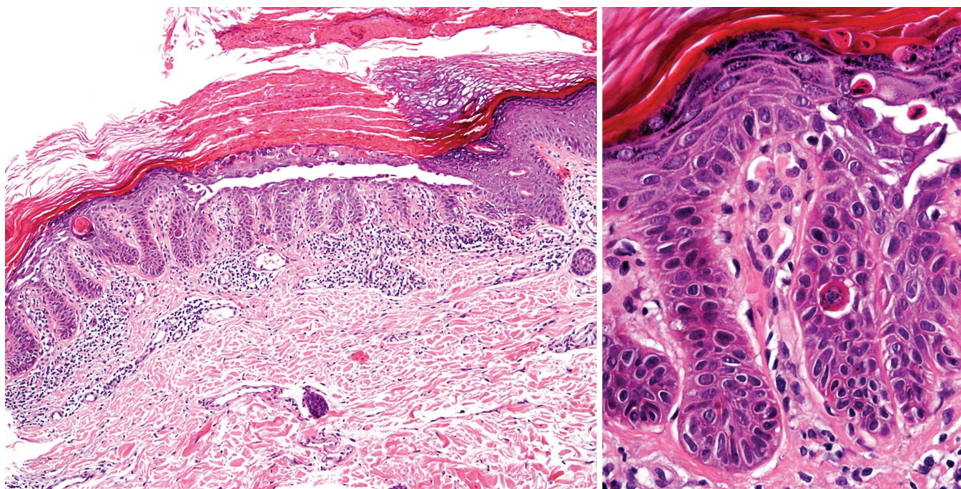


Figure 23.11 Galli–Galli disease. Filiform proliferation of rete ridges, basal hyperpigmentation, and acantholytic dyskeratosis.

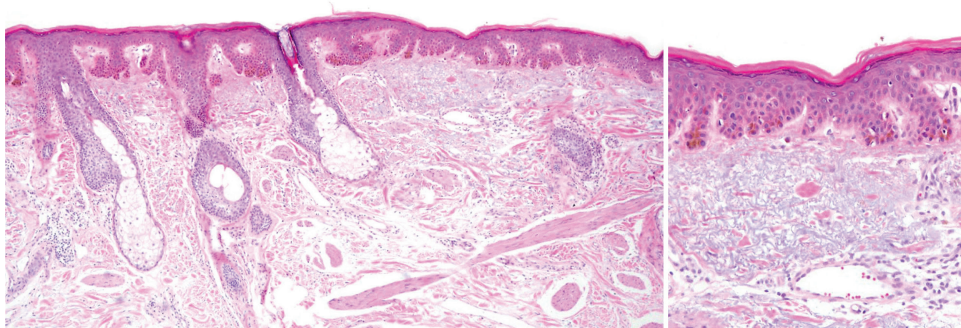


Figure 23.12 Solar lentigo. Fingerlike projections of the epidermis, hyperpigmentation of the basal layer, and solar elastosis in the dermis.

with melanoma in situ (type lentigo maligna), because all of them are the result of chronic sun damage. Solar lentigo is not a “precursor lesion” of any type of melanoma, but it is an entirely benign keratinocytic neoplasm. Sometimes, solar lentigo may undergo regression in the form of lichen planus–like keratosis. In that setting, a band-like lymphocytic infiltrate obscures the dermoepidermal junction, a jagged appearance of the epidermis with basal necrotic keratinocytes may be present, and melanophages can be found in the superficial dermis.

Seborrheic keratosis

Seborrheic keratosis is a very common pigmented acanthoma that occurs in the adult population. The lesions commonly occur on the trunk, in the big folds, and on sun-exposed surfaces of the face and extremities, but they spare palms and soles. The clinical appearance and histopathology can be variable in regard to the amount of hyperkeratosis and acanthosis, but all lesions show at least some acanthosis and at least hyperpigmentation of basal keratinocytes.^{27,28} Usually, basaloid, as well as squamoid, differentiation of keratinocytes is seen, but the proportion of both varies in the different types of seborrheic keratosis. Melanocytes are present, but regularly distributed and with no formation of nests. On sun-damaged skin, seborrheic keratosis commonly presents with reticulated acanthosis (so-called adenoid seborrheic keratosis), and it is commonly seen in continuity with solar lentigo. Just as solar lentigo, seborrheic keratosis may undergo regression in the form of lichen planus–like keratosis.

Dermatosis papulosa nigra

Dermatosis papulosa nigra is a condition seen on the face of patients with dark skin types. Small pigmented papules are found on both cheeks in the periorbital region, but also on the neck. Histologically, the changes are almost indistinguishable from those of seborrheic keratosis, but the keratinocytes show squamoid differentiation, while basaloid differentiation is absent.^{3,29} The architecture of the lesion is often reticulated.

Epidermal nevus

An epidermal nevus is a congenital malformation in which the epidermis is thickened and variably verrucous.³⁰ The papillary dermis is expanded so that papillomatous lesions may develop in the affected area. The epidermis is often slightly hyperpigmented, but melanocytes are not increased in number. In a biopsy, changes of epidermal nevi are very similar to those of acanthosis nigricans or seborrheic keratosis, so that clinical correlation is necessary to confirm the diagnosis.

Late-stage morphea

In some patients with morphea, the lesions develop accompanying epidermal hyperpigmentation. The clinical appearance is that of an indurated, depressed, sclerotic patch. Histopathologically, pigmentation is seen in the basal layer of the epidermis.^{3,31} Some melanophages may be present in the papillary dermis. The dermis shows typical changes of morphea with thickened bundles of collagen and variable perivascular and interstitial infiltrates of lymphocytes (Figure 23.13).

Dermatofibroma

Dermatofibroma is a common benign fibrohistiocytic lesion that is considered to develop as a reaction to an insect bite or other focal trauma. Clinically, it presents as an indurated nodule with an often hyperpigmented surface. The hyperpigmentation corresponds to increased pigmentation of basal keratinocytes, which is often accompanied by acanthosis or seborrheic keratosis–like changes.³² The epidermal changes above dermatofibroma occasionally also include induction of follicular or sebaceous adnexal structures. They are considered to result from mediators released by fibroblasts that interact with epidermal cells.

Mastocytosis

A number of conditions with diverse clinical appearances are typified histologically by an increase in mast cells in the superficial dermis. The clinical presentation may be that

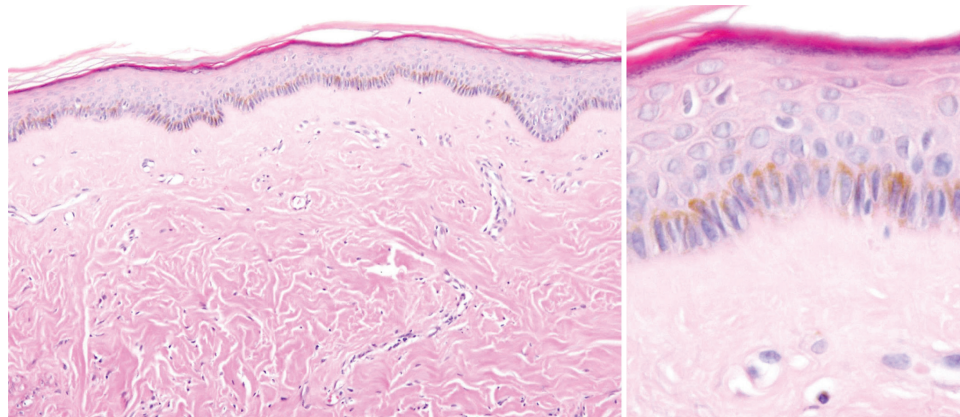


Figure 23.13 Morphea. Hyperpigmentation of the basal layer, together with thickened bundles of collagen and perivascular and interstitial infiltrates of lymphocytes.

of urticaria pigmentosa, telangiectasia macularis eruptive perstans, diffuse cutaneous mastocytosis, or solitary mastocytoma. In all these conditions, the epidermis overlying the mast cell infiltration often shows increased pigmentation in the basal layer (Figure 23.14).³³ The number of melanocytes, however, is normal. Epidermal pigmentation, as well as eosinophils in the dermal infiltrate, are a clue to consider a diagnosis of mastocytosis. The number of mast cells in the tissue is usually high in mastocytosis of childhood and in mastocytoma, while the increase are often moderate in adult mastocytosis. Special stainings with Giemsa, tryptase, or CD117 antibodies (c-kit) help to identify mast cells in the tissue.

Notalgia paraesthetica

Notalgia paraesthetica results from damage of thoracic nerves that is followed by localized itch, usually on the upper back.³⁴ The clinically pigmented patches show only mild changes on microscopy. There are melanophages in the upper dermis and maybe some hyperpigmentation of the basal layer. In addition, some compact orthokeratosis and individual dyskeratotic keratinocytes in the mid- and upper spinous layer may be encountered.

PIGMENTATION IN THE DERMIS OR DEEPER TISSUES

The most common cause of pigmentation in the dermis is melanophages, which may be found at a late, resolving stage of a number of conditions, such as lichen planus, fixed drug eruption, or prurigo pigmentosa. In this context, those melanophages may be accompanied by epidermal hyperpigmentation and acanthosis. Other frequent causes of dermal pigmentation are extravasated erythrocytes and hemosiderophages, e.g., in pigmented purpuric dermatosis or stasis dermatitis. However, dermal pigmentation may also be caused by pigmented dendritic melanocytes in the dermis, as is the case in nevus of Ota, or by deposits, as seen in primary and secondary ochronosis or exogenous pigmentation.

Postinflammatory hyperpigmentation

Postinflammatory hyperpigmentation can be seen in numerous conditions, and the intensity of it varies with skin type. Conditions that are almost always followed by hyperpigmentation are fixed drug eruption and phototoxic dermatitis. Postinflammatory hyperpigmentation may consist of two components, increased epidermal pigmentation and melanophages in the dermis (Figure 23.15).^{3,35}

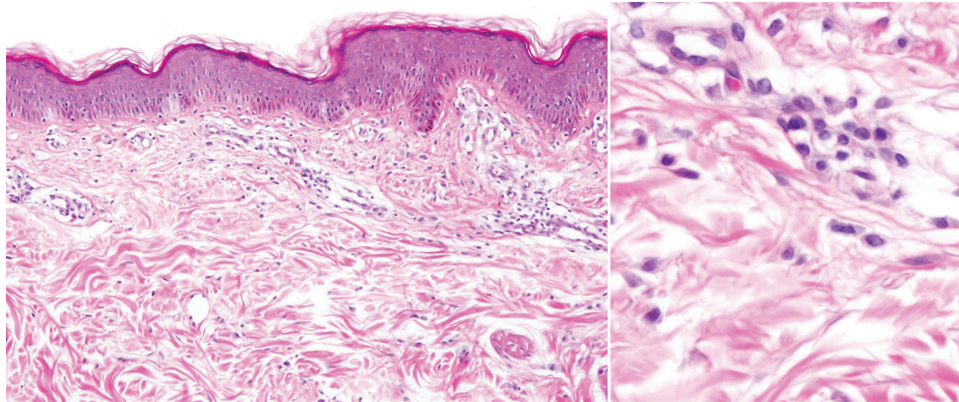


Figure 23.14 Mastocytosis. The epidermis overlying the mast cell infiltration shows increased pigmentation in the basal layer.

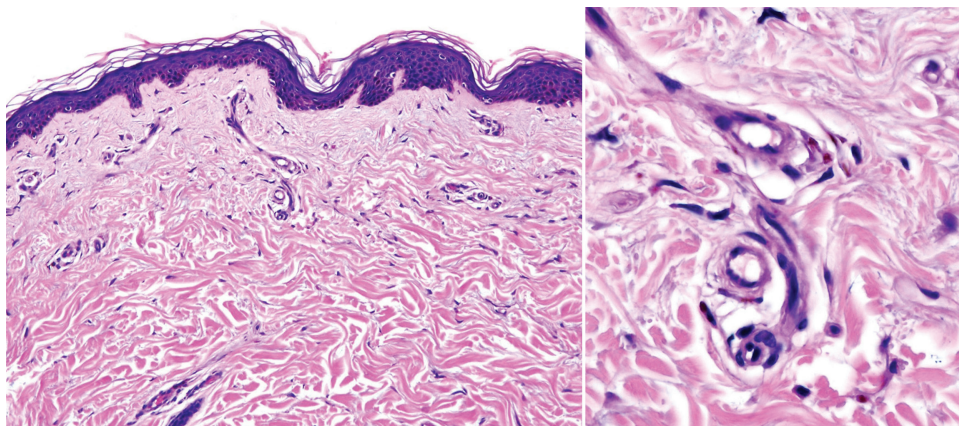


Figure 23.15 Postinflammatory hyperpigmentation. Basal hyperpigmentation and melanophages around the superficial plexus.

While epidermal hyperpigmentation resolves relatively quickly, melanophages in the dermis may stay for weeks and months.

Ashy dermatosis (erythema dyschromicum perstans)

Blue-gray patchy pigmentation on the back of patients with darker skin types is the typical clinical appearance of what is called ashy dermatosis. The condition is somewhat controversial but is now widely considered to be a form of late lichen planus.^{3,35,36} Histopathologically, there is an atrophic epidermis with flattened rete ridges, basal vacuolar alteration, and necrotic keratinocytes in the basal layer. A band-like lymphohistocytic infiltrate may be present in the superficial dermis. Melanophages are present in the superficial dermis but also in deeper perivascular location.

Prurigo pigmentosa, late

Prurigo pigmentosa is a condition of unknown etiology that was first described in the Japanese population. It presents with hive-like itchy papules and plaques that are short-lived and resolve within a week, leaving behind reticulate pigmentation. The chest, back, and neck are the sites of predilection.^{37–39} While histopathologic findings early in the course are diagnostic (intraepidermal neutrophils, necrotic keratinocytes, ballooning, and band-like lymphocytic infiltrate), just slight acanthosis and melanophages are seen at the resolving pigmented stage (Figure 23.16). Lesions tend to recur at the same sites, and with each recurrence, melanophages may be encountered deeper in the dermis, just as is also the case in recurrent lesions of fixed drug eruption.

Macular amyloidosis

Macular amyloidosis is a form of cutaneous amyloidosis that does not show systemic involvement. It is closely related to lichen amyloidosis, and changes of both clinical manifestations may appear together in the same patient.^{3,35,40} Macular amyloidosis presents as hyperpigmented and rippled patches on the trunk, and it is

heavily pruritic. On microscopy, macular amyloidosis shows changes of lichen simplex chronicus, together with deposits of cytokeratin amyloid in the papillary dermis and some melanophages. Cytokeratin amyloid can be highlighted immunohistochemically with pan cytokeratin antibodies.

Incontinentia pigmenti, late

Incontinentia pigmenti is a genodermatosis inherited in X chromosomal dominant fashion. The mutation has been located in the NEMO gene (Xq28, NF-kappa B).⁴¹ The condition affects only girls, except rare mosaicism or Klinefelter syndrome, and it manifests itself shortly after birth. The clinical features pass through typical stages with erythematous vesicles (1–4 months), hyperkeratotic plaques (2–6 months), hyperpigmentation (7 months to 12 years), and hypopigmented atrophic lines (6 years to adulthood). In approximately 80% of all patients, the genodermatosis also affects other organs, such as the eyes, teeth, central nervous system (CNS), skeleton, and heart. The prognosis chiefly depends on the degree of CNS involvement. The histopathologic findings of incontinentia pigmenti vary according to the stage in the process: At the beginning, spongiotic vesicles are joined by intraepidermal eosinophils and dyskeratotic cells, combined with a superficial perivascular infiltrate dominated by eosinophils. Later, hyperkeratosis, hyperplasia, and papillomatosis develop and dyskeratotic cells of various numbers can be found at all levels of the epidermis (Figure 23.17). At a late stage, melanophages are present in the papillary dermis.⁴² Even in adulthood, necrotic keratinocytes in the epidermis or dermis are a clue to the diagnosis of incontinentia pigmenti, but at that stage, melanocytes are reduced in number, some fibrosis is found in the dermis, and hair follicles are atrophic.

Pigmented purpuric dermatoses

Pigmented purpuric dermatoses are a group of conditions with variable clinical findings and quite similar histopathologic changes. The clinical variants include

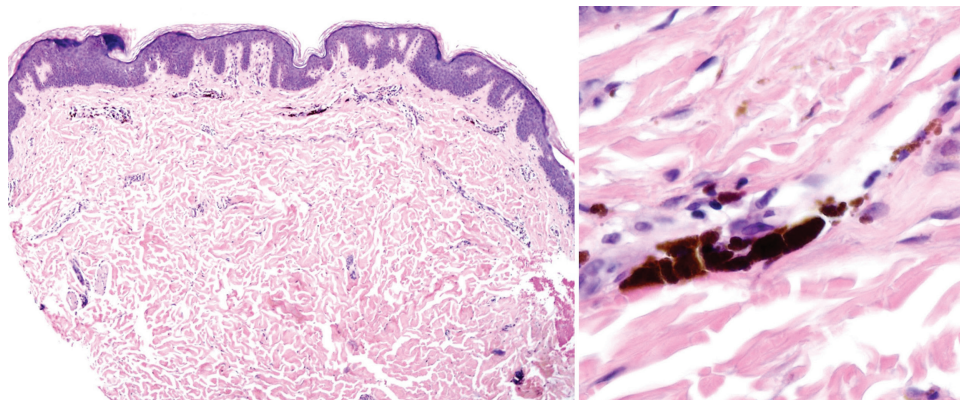


Figure 23.16 Prurigo pigmentosa, late stage. Slight acanthosis and marked infiltrates of melanophages around the superficial plexus.

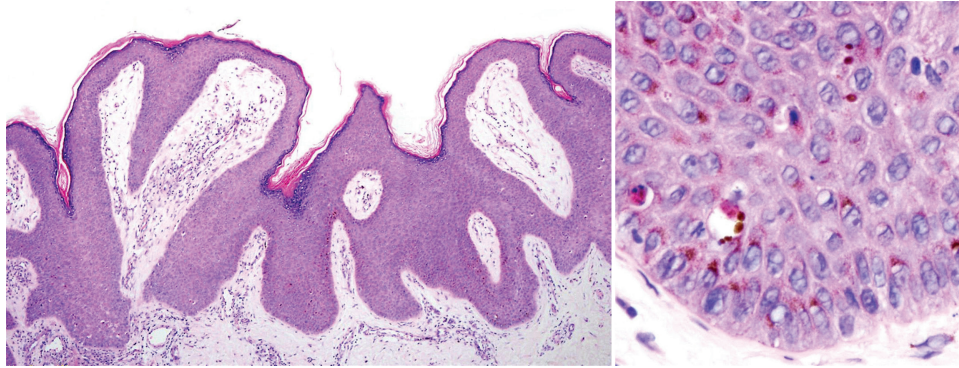


Figure 23.17 Incontinentia pigmenti, late. Papillomatosis, hyperpigmentation of epidermal keratinocytes, and a few dyskeratotic cells.

Schamberg's disease (mottled pigmentation and purpuric macules on the legs), eczematid-like purpura (similar to Schamberg's disease, but with scaling surface), annular purpura of Majocchi (annular patches and telangiectasia), lichenoid purpura of Gougerot and Blum (lichenoid papules coalescing to plaques on the legs), and lichen aureus (orange-brown patches). Histopathologic findings are those of a perivascular and/or band-like infiltrate of lymphocytes with variable amounts of extravasated erythrocytes and hemosiderophages (Figure 23.18).^{3,35} Sometimes, granulomatous features may be present.⁴³ The epidermis shows no or very little changes in the form of spongiosis. Hemosiderophages in the dermis can be highlighted by an iron staining, such as Berlin blue or Perl's. In very long-standing lesions, alteration of the collagen in the form of wiry bundles can be observed in the superficial dermis.

Hemochromatosis

Hemochromatosis is a condition in which iron accumulates in the body. Hereditary hemochromatosis is caused by a C282Y mutation in the human hemochromatosis gene

(HFE gene), but similar signs and symptoms may develop consequent to repeated blood transfusions.^{44,45} Typical clinical signs are liver cirrhosis, diabetes, cardiomyopathy, arthritis, testicular failure, and discoloration of the skin, especially the face. Histopathologically, the epidermal melanin pigmentation is increased in the basal layer and hemosiderin deposits can be found in the epidermis, as well as the dermis. Golden-brown granules of hemosiderin may also be seen in the basement membrane region of sweat glands and in macrophages in the adventitial dermis of eccrine structures.

Nevus of Ota, nevus of Ito, and Mongolian spot

Nevus of Ota and nevus of Ito are melanocytic hamartomas that present clinically as a blue-gray discoloration.^{3,9,13} Nevus of Ota is located in the ophthalmic and maxillary branches of the trigeminal nerve and may also involve conjunctiva or oral mucosa. Nevus of Ito is found in the shoulder area. Histopathologically, fine bipolar dendritic melanocytes are scattered in the dermis. Similar changes are also seen in Mongolian spots, which are typically located on the sacral region of a newborn.

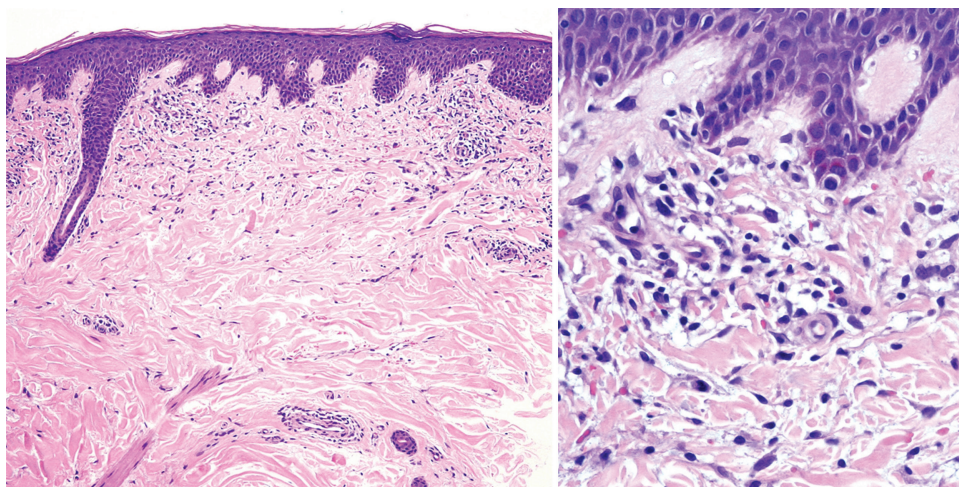


Figure 23.18 Schamberg's disease. Perivascular and band-like infiltrate of lymphocytes, together with extravasated erythrocytes.

Ochronosis (alkaptonuria)

Inherited ochronosis (alkaptonuria) is caused by a defect in the enzyme homogentisic acid oxygenase, which inhibits the metabolism of homogentisic acid. Intermediates of homogentisic acid bind to collagen fibers of skin and cartilage. The skin shows gray or black macules and patches on the face, neck, and distal extremities. Bluish discoloration of the sclerae and of the cartilage of the ears, and sometimes of the nose, may also be present. Histopathologically, the fibers are orange, and in the skin they may fill the entire dermis (Figure 23.19).^{3,46}

Exogenous ochronosis

Exogenous ochronosis is a disease of patients with darker skin types. It develops after prolonged usage of skin bleaching products that contain hydroquinone. Patchy grayish hyperpigmentation develops in the affected areas. On histopathology, the picture is very similar to that seen in alkaptonuria. Orange fibers of bizarre configuration are seen in the dermis (Figure 23.20).⁴⁷ The exact pathomechanism is unknown, but it is assumed that hydroquinone inhibits the homogentisic acid oxygenase.

Minocycline hyperpigmentation

Various medications, such as antimalarial drugs, phenothiazines, tetracyclines, and minocycline, may induce pigmentary alterations. Apart from pigment deposition in macrophages and dermal dendrocytes, characteristic patterns of pigmentation have been attributed to minocycline.^{3,48} In some cases, pigment is seen along the elastic fibers (Figure 23.21); in others, myoepithelial cells contain pigment.

Argyria

Argyria develops when silver salts are deposited in the body. Today, silver is ingested as part of silver-decorated sweets or in alternative health treatments. The skin shows blue-gray pigmentation, which is most extensive in sun-exposed areas. The pigmentation is probably due to silver metal and silver sulfides, which develop after sun exposure from silver salts. Microscopically, black granules deposited close to the basement membranes of sweat glands and hair follicles and along elastic fibers in the papillary dermis are typical.^{40,49} Identification of the deposits may be facilitated by dark-field microscopy. Moreover, melanin

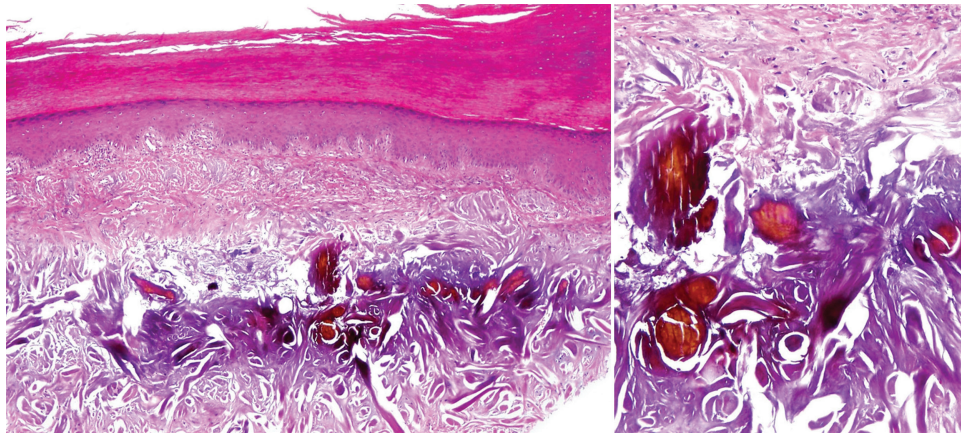


Figure 23.19 Ochronosis (alkaptonuria). Orange fibers in the dermis.

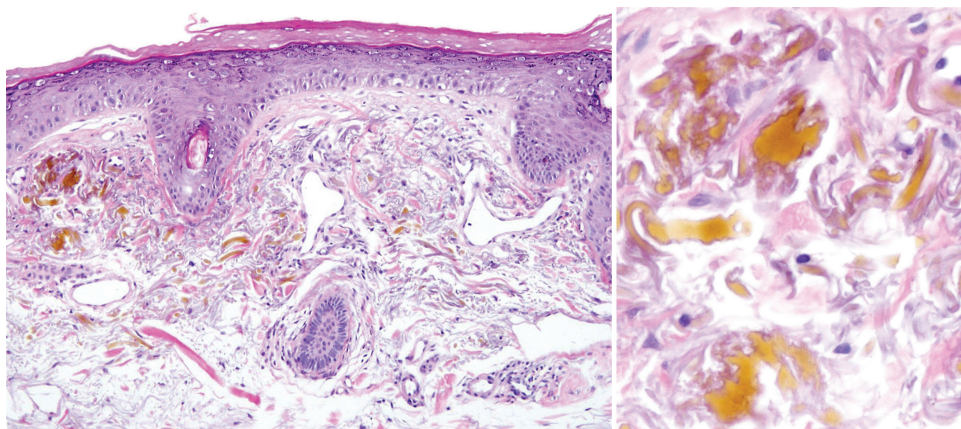


Figure 23.20 Exogenous ochronosis. Orange fibers in the dermis.

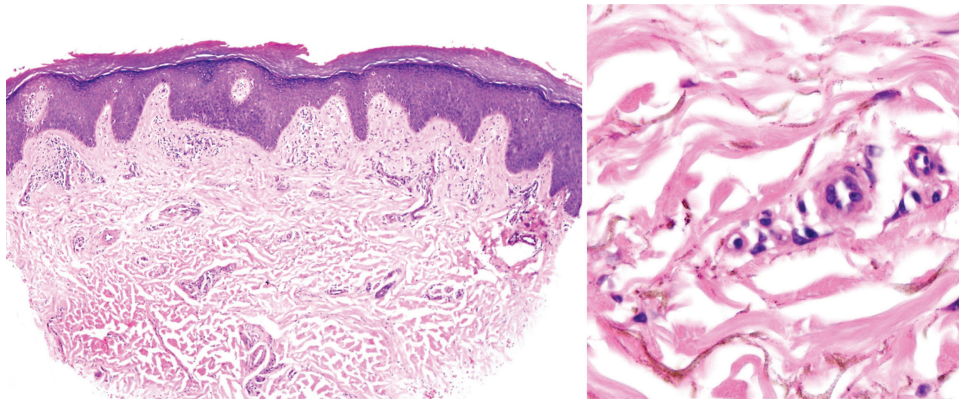


Figure 23.21 Minocycline hyperpigmentation. Pigmentation along the elastic fibers.

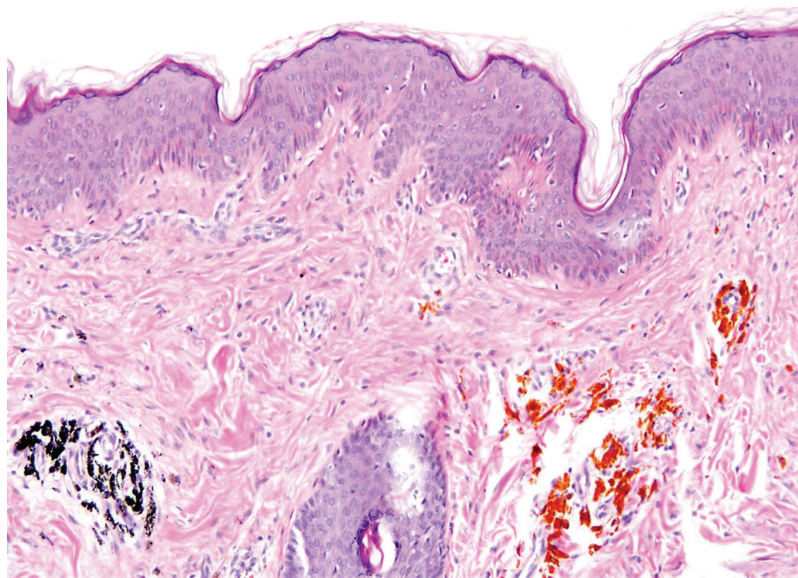


Figure 23.22 Tattoo. Pigmented globules in the dermis.

pigmentation of the epidermal basal layer is increased and melanophages are seen in the papillary dermis.

Tattoo

Tattoos are made by mechanical transportation of exogenous pigment into the dermis. Besides the artistic deliberate creation of tattoos, similar changes also develop after excoriation trauma with contact with tar products or other pigmented substances, or after dentist treatment with amalgam. The ink of tattoos can easily be identified in the tissue as either free globules or fragments or incorporated in macrophages (Figure 23.22). While dark pigment is readily visualized, red colors are somewhat harder to recognize because there is little contrast to the pink-stained collagen fibers. Tattoo-related complications include infections and hypersensitivity reactions with eczematous, granulomatous, lichenoid, and pseudoepitheliomatous patterns.⁵⁰ A skin biopsy is often helpful in the differential diagnosis of tattoo reactions.

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Reflectance confocal microscopy

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and GIOVANNI PELLACANI

INTRODUCTION

In vivo reflectance confocal microscopy (RCM) is a non-invasive optical imaging technique that provides high-resolution images of skin. RCM relies on a low-power laser that emits near-infrared light (830 nm).¹ To attain a lateral resolution of about 1 micron, RCM allows only light back-reflected from a desired focal point within the skin to pass back through a gating pinhole and enter the detector. The basic RCM optical section image is comparable to high-magnification histopathology at about 330 $\times$; the advantage of RCM compared with histopathology is that optical sections can be obtained *in vivo*, with no disruption of the skin. Output images are horizontal and parallel to the surface of the skin, visually sectioned in a manner resembling histopathologic specimens in Mohs micrographic surgery.

RCM can image the epidermis and papillary dermis but is limited to an imaging depth of about 200 microns, which is enough to explore superficially located skin diseases.

RCM has been applied to evaluate melasma and for treatment monitoring.²⁻¹³ Furthermore, correlation of histopathology and RCM findings in melasma has been studied.^{5,6}

RCM FINDINGS IN MELASMA

Kang et al. recruited 26 patients with facial hyperpigmentation.⁵ RCM examination of melasma lesions and the adjacent skin was performed, and RCM images were acquired at three levels: the suprabasal layer, dermoepidermal junction, and dermis. Biopsies were obtained from eight patients.

RCM features of melasma in the epidermis revealed a hyperrefractile cobblestone pattern in the basal cell layer and occasionally in the lower stratum spinosum, compared with the normal surrounding area. The presence of this cobblestone pattern was correlated histologically to increased melanin content in the keratinocytes. Most of the patients also showed an abrupt transition from the stratum spinosum to the papillary dermis upon RCM, corresponding to flattened rete ridges in all the biopsy specimens. Five out of 26 patients with preserved rete ridges showed brighter papillary rings. Furthermore, 6 out of 26 patients showed the presence of bright dendritic cells at the level of the dermoepidermal junction. These cells were immunohistochemically identified as activated melanocytes. RCM imaging of the upper dermis showed plump bright cells in 9 of 26 patients, which corresponded to melanophages. In four out of these nine patients, scattered melanophages were detected, partly explaining the uneven distribution of melanin

in a given melasma region. Finally, an increased number of vessels in melasma appeared as dark, round to tubular structures within the papillary dermis in RCM imaging.⁹

Liu et al. enrolled 210 patients with facial melasma.⁶ In 10 of these patients, skin biopsies were performed at the same site of RCM examination, revealing an increased amount of melanin in the epidermis compared with the perilesional skin. The hyperpigmentation of the epidermis corresponded to highly refractile keratinocytes distributed in the spinous layer. RCM examination of the dermoepidermal junction revealed strongly visible papillary rings around the dermal papillae, composed of a sequence of bright cellular structures or a hyperrefractile cobblestone pattern in the flattened basal cell layer, mostly seen on the forehead and upper lips. Notably, all specimens showed increased melanin in all epidermal layers, and few had melanin in the dermis, enhancing the claim that there is actually no true dermal type of melasma.⁶

RCM examination has also been used for the evaluation of treatment response in melasma. Ardigo et al. conducted a study in order to investigate RCM features of melasma within the epidermis and upper dermis and assess the usefulness of the technique in treatment monitoring.⁴ Researchers enrolled 15 patients with facial melasma and matched them with a control group of 10 patients. Concerning the distribution of pigment within skin layers, their findings were in line with previous literature data. Specifically, an increased degree of epidermal pigment was seen as highly refractile keratinocytes with prominent nuclei at the level of the stratum spinosum. Activated melanocytes and junctional keratinocytes receiving packed melanosomes were detected at the dermoepidermal junction, appearing as strongly visible papillary rings around the dermal papillae composed of a sequence of brighter cellular structures. In the upper dermis, several melanophages with haphazard distribution were detected. The role of possible Langerhans cells was proposed for dendritic cellular structures found in the spinous layer in 5 out of 15 patients, although histopathologic correlation was not provided. All patients treated with a combination of a chemical peel of 50% pyruvic acid and a topical application of Kligman's formula containing 2% hydroquinone showed a good treatment response as assessed by RCM, which revealed a decreased brightness. In detail, RCM revealed a reduction of pigmented bright keratinocytes within the epidermis and a major decrease in brightness around dermal papillae in two out of five patients, while the rest had a significant clinical improvement, but still

showed small traces of pigment. Concerning the dermal compartment, the results were less enthusiastic, with a partial reduction in the number of melanophages.

Our group evaluated the efficacy of low-energy Q-switched laser treatment of melasma by means of RCM.⁷ Eight female patients with facial melasma were recruited and subjected to low-energy Q-switched Nd:YAG laser (1064 nm) treatment. In total, nine laser sessions were performed. Confocal examination took place at baseline, after five and nine sessions. Clinically, all patients improved and RCM confirmed the efficacy of this type of laser treatment for melasma. In particular, baseline RCM features corresponding to epidermal hyperpigmentation included a honeycombed pattern, as well as a mottled pigmentation of a cluster of bright keratinocytes in three cases (Figure 24.1).^{3,8} Bright dendritic perifollicular cells were detected in one case. At the dermoepidermal junction, all cases showed bright polycyclic contours and bright hair follicles or rings, which correspond to the pigmented keratinocytes and melanin-rich melanocytes located at the basal and suprabasal layers of an elongated rete ridge. The authors highlight these findings as a biologic response of the skin to the ultraviolet (UV) injury, which plays an important role in the development and maintenance of melasma. In the superficial dermis, no RCM features of melasma were observed.

After nine laser sessions, neither mottled pigmentation nor polycyclic papillary contours were detected, confirming the obvious clinical improvement. However, three cases showed dendritic-shaped cells with a bright body cell and peripheral branching structures focally distributed around hair follicles, and interestingly, these were the cases presenting with a relapse of melasma after 3 months of follow-up.⁷

Goberdhan et al. assessed the efficacy of a superficial chemical peel combined with a multimodal, hydroquinone-free brightener, using RCM in three patients, thus also confirming the reliability of confocal analysis for the evaluation

of treatment in melasma.⁸ Tsilika et al. conducted a clinical trial in 10 patients assessing a nonhydroquinone topical bleaching agent, by means of RCM.⁹ The authors report a discrepancy between Wood's lamp and RCM classification of melasma at the treatment baseline. After 1 month of treatment, there was concordance between clinical improvement and RCM findings, particularly a substantial decrease of the hyperrefractile cobblestone epidermal pattern. A partial clinical response was reported for patients with melanophages observed within the dermis by means of RCM.⁹ Costa et al. reported a case of melasma presenting bright dendritic cells within the epidermis and bright irregularly shaped structures among bundles of collagen in the superficial dermis, corresponding to activated melanocytes and melanophages, respectively.¹⁰ Funasaka et al. reported similar RCM findings in one case of melasma.¹¹ Zhou et al. performed RCM examination in 6 out of 50 melasma patients who were treated by Q-switched Nd:YAG laser (1064 nm). RCM findings confirmed previously published data, confirming the usefulness of *in vivo* confocal analysis in the evaluation of melasma treatment.¹²

CONCLUSIONS

RCM is an excellent imaging tool that can be applied successfully to diagnose skin diseases such as melasma and for treatment monitoring. In fact, the possibility to explore the skin at a cellular resolution, without leading to scar formation, as occurs in routine skin biopsy, is a step forward to deepen knowledge of a given disease while providing *in vivo* findings that can be monitored over time. As a limitation, RCM readers face the challenge of distinguishing between cells with a similar reflection index and shape, such as Langerhans cells versus dendritic melanocytes at the spinous layer. Moreover, the cost of the current devices and the training and experience needed for RCM-based analysis may be additional barriers to the adoption of this technology.

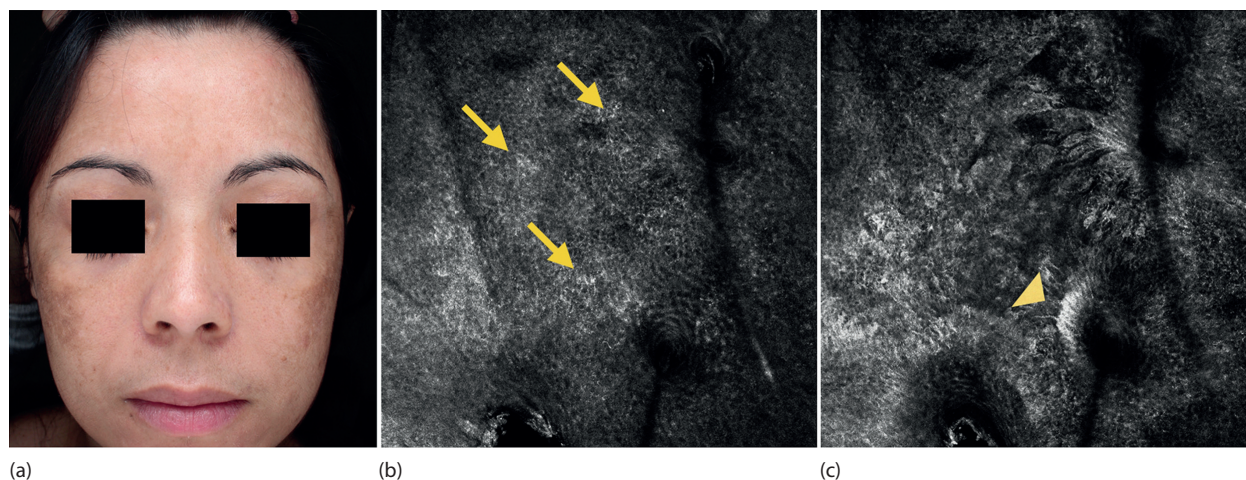


Figure 24.1 (a) Clinical image of a female patient in her thirties with moderate melasma. (b) An RCM high-resolution image shows the presence of bright spots mixed with dendritic cells (arrows). (c) RCM at the dermoepidermal junction level reveals the presence of bright dendritic cells corresponding to melanin-laden melanocytes.

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INTRODUCTION

Assessment of skin colors is crucial for the diagnosis, management, and therapeutic outcome evaluation of hyperpigmentary disorders.

In this regard, naked-eye and dermoscopic examination remain the gold standard techniques, but are affected by high interobserver variability; in fact, although the human eye can distinguish colors as accurately as any specific device when observed simultaneously, qualitative and repetitive assessments are only reliable with objective measurements.¹

To address this issue, reflectance spectroscopy techniques, which include colorimetry and spectrophotometry, have been introduced in the clinical setting. They represent objective and reproducible methods for the evaluation of skin colors, based on the measure of the intensity of reflected light of specific wavelengths.² In colorimetry methods, handheld tristimulus reflectance colorimeters are employed, such as the Photovolt ColorWalk colorimeter (Photovolt Instruments, Minneapolis, Minnesota) and the Minolta Chromameter (Minolta, Osaka, Japan), while for spectrophotometry, narrowband reflectance spectrophotometers are used, such as the DermaSpectrophotometer (Cortex Technologies, Hadsund, Denmark) and Mexameter (Courage&Khazaka, Cologne, Germany).³ Furthermore, spectrophotometric intracutaneous analysis (SIAscopy) is a novel diagnostic method with a higher accuracy in determining the contribution of individual skin chromophores.⁴

Several applications of reflectance spectroscopy in clinical practice have been established, including evaluation of pigmentary disorders and pigmented skin lesions, phototype assessment, quantification of the bleaching effect of depigmenting agents, and measurement of ultraviolet (UV)-induced pigmentation and chronobiological skin color variation.⁵

TRISTIMULUS REFLECTANCE COLORIMETRY

Tristimulus instruments produce a white light that interacts with a chosen skin area and then records the intensity of reflected light through a photodiode array.

The results are mainly expressed with the Commission International d'Eclairage (CIE) Lab color system, which describes colors by their lightness value (L^*) and the amount of green or red (a^*) and amount of yellow or blue (b^*) they contain.²

The L^* value expresses the relative brightness of color (ranging from black to white) and, along with the b^* value, is used to measure pigmentation; the a^* value best captures erythema or skin redness.³

NARROWBAND SPECTROPHOTOMETERS

Narrowband instruments use light-emitting diodes for green light (565–568 nm) and red light (635–670 nm and 880 nm) to illuminate the skin surface, and then the intensity of the reflected light is measured.¹

These devices can identify the presence of the two main cutaneous chromophores, melanin and hemoglobin, as they show different spectral curves for light absorption, with a large peak in the green wavelengths and little absorption in the red ones for hemoglobin, and absorption of all wavelengths for melanin. Therefore, the reflectance of narrowband light in the red spectrum would yield a reasonable estimate of the melanin content of a subject's skin. The degree of skin redness or erythema is calculated by subtracting the absorbance due to melanin from the absorbance of the green filter.

Data are expressed in terms of erythema (E) and melanin (M) indices, which increase as the skin becomes more erythematous and more pigmented, respectively. However, the erythema index is also influenced by the melanin index, and vice versa, as strong erythema may significantly decrease the melanin index.⁶

TRISTIMULUS COLORIMETRY VERSUS NARROWBAND SPECTROPHOTOMETERS

Previous studies compared tristimulus colorimetry and narrowband reflectance spectrophotometry.

Clarys et al.⁷ evaluated the use of three instruments: the Minolta Chromameter, the Mexameter, and the DermaSpectrophotometer. They demonstrated a good day-to-day repeatability in melanin measurement (1% variability) for the first two devices, but poor repeatability for the third one (4% variability). All instruments were effective at quantifying even small changes in skin color. In addition, the Chromameter was shown to be capable of measuring all colors, whereas the reflectance spectrophotometers are designed to measure only the intensity of erythema and melanin-induced pigmentation.

Shriver and Parra⁸ compared the use of the Photovolt ColorWalk colorimeter and the DermaSpectrophotometer in the determination of skin and hair color in 80 subjects from different ethnic groups, showing a strong correlation between L^* and M indices; however, the relationship between a^* and E indices was complex and dependent on the pigmentation level.

Although both devices provided accurate measurements of pigment levels in skin, the narrowband instrument readings were less affected by the greater redness of certain body sites due to the degree of vascularization.

SIASCOPY

Human skin color is dependent almost exclusively on the concentration and spatial distribution of two chromophores: melanin and hemoglobin, with the former being the most relevant.⁹ Reflectance spectroscopy techniques provide objective measurement of skin colors, but they are not able to fully separate the contributions of individual chromophores. SIAscopy holds the promise to overcome this issue by performing an *in vivo* quantification of the concentration and distribution of eumelanin, oxyhemoglobin, and dermal collagen.¹⁰

The device emits harmless radiation, ranging from 400 to 1000 nm, and then measures the reflected light for each wavelength.¹¹

The SIA technique creates a high-resolution composite white light image and provides additional, mutually exclusive chromophore maps that display the concentration of melanin and hemoglobin in the epidermis and collagen and melanin in the papillary dermis, pixel by pixel. Although it cannot replace the standard of care in skin cancer diagnosis, represented by clinical examination and dermoscopy,⁴ SIAscopy has been shown to have good sensitivity and specificity levels in the detection of melanoma and nonmelanoma skin cancers, and can be readily applied to the evaluation of hyperpigmentary disorders as well.^{12,13}

SPECTROPHOTOMETRY AND HYPERPIGMENTARY DISORDERS

Hyperpigmentary disorders occur with greater frequency and severity in black individuals and mostly involve the face, with melasma being the most common.¹⁴

The diagnosis of melasma is mainly based on anamnestic, naked-eye, and dermoscopic assessments, but these methods do not allow us to precisely quantify the clinical severity and therapeutic outcome. Several tools have been created and used for this purpose, such as the Melasma Area and Severity Index (MASI) score, visual hyperpigmentation scales, UV light, polarized light photography, confocal microscopy, and reflectance spectroscopy.³ Among these, reflectance spectroscopy is the only method that allows an objective quantification of the amount of melanin in the skin, representing a very useful tool for clinical severity and therapeutic outcome assessment in melasma; both tristimulus reflectance colorimeters and narrowband spectrophotometer devices have been used.¹⁵

CONCLUSIONS

The use of pectrophotometry in hyperpigmentary disorders holds the promise to objectively and rapidly quantify the amount of “color” in terms of melanin and hemoglobin. Further studies on a larger basis are warranted to test the sensitivity and specificity of these devices while highlighting possible limitations and confounders.

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INTRODUCTION

Disorders of hyperpigmentation can be congenital or acquired, diffuse or localized. Color variation may be an important clue to the diagnostic procedure. The most common hyperpigmentation disorders due to genetic factors are presented in Table 26.1, while acquired hyperpigmentation disorders are presented in Table 26.2, along with the typical color presentation. The most common diagnoses of localized hyperpigmentation are melasma and postinflammatory hyperpigmentation. The most common diagnosis of diffuse hyperpigmentation is hyperpigmentation associated with endocrine disorders or drug-induced hyperpigmentation. The epidemiology of hyperpigmentation disorders in a particular region, the clinical characteristics of hyperpigmentation, and a thorough history of the patient will be enough to get a diagnosis in most cases. Histopathology will confirm the diagnosis or provide useful insight on the main disorder in the case of secondary hyperpigmentation. Dermoscopy of hyperpigmented lesions is useful to avoid a biopsy in cosmetically critical areas, such as the face. Examination under Wood's lamp can determine the depth of melanin deposition and level of treatment success.

EPIDEMIOLOGY

The range of prevalence of various hyperpigmentation disorders among different geographical regions, races, and sexes might offer useful information in the diagnostic process. The most common localized acquired hyperpigmentation is melasma. Even though melasma is observed within all racial and ethnic groups, it is more common in individuals with higher skin phototypes living in areas of intense ultraviolet (UV) radiation, especially in Latin Americans, Asians, and Africans.¹ Similarly, it is more common in young women, with men accounting for about 10% of all cases.² Pigmentary demarcation lines (PDLs) occur in all races and can be observed even in lighter skin types. The prevalence of PDLs in women has been reported to vary from 14% in Saudi Arabia to 79% in the United States in African Americans.^{3,4} Incontinentia pigmenti affects girls in 97% of the cases. Men with incontinentia pigmenti may have Klinefelter syndrome or mosaicism.⁵ Erythema dyscromicum perstans is almost exclusively observed in Hispanics.⁶ Poikiloderma of Civatte commonly affects fair-skinned individuals, starting in the fourth decade of life, especially in postmenopausal women.⁷

CLINICAL FINDINGS

Localized hyperpigmentation

Melasma is an irregular hyperpigmentation that mostly affects the forehead, temples, cheeks, and upper lip. PDLs

might be observed between the lateral and medial aspects of the upper arm, on the central chest, on the midback, and on the face on the lateral cheek and periorbital skin.

PDLs can be distinguished from melasma because they are symmetrical, follow the Blaschko lines, and in many cases, are present since infancy.

Mechanical hyperpigmentation can be observed on the skin at the belt line, under brassiere straps, or under backpack straps. In addition, the groin axilla and neck are common sites of hyperpigmentation in overweight individuals, attributed to chronic friction of skin flaps.

In poikiloderma of Civatte, the pigmentation is reticulated, reddish to brown, with irregular and symmetrical distribution, affecting the hemifaces, neck, and upper third of the chest, and sparing the shaded chin area. It is frequently accompanied by superficial atrophy and telangiectasias.

Acanthosis nigricans appears as hyperchromic plaques, with vegetative, lichenified, or papillomatous surfaces, dark brown to black coloration, located in the armpits, groin, neck, and other intertriginous areas.

Postinflammatory hyperpigmentation might affect any area and assume any shape in patients with chronic lesions of various dermatoses. Typical examples include acne papule hyperpigmentation on the face, lichen planus hyperpigmentation on the dorsal aspect of the hands, and zosteriform hyperpigmentation on the torso, while hyperpigmentation due to lichen simplex chronicus might involve any body area.

Reticulated hyperpigmentation of the shins and inner aspects of thighs is typical of erythema ab igne.

Blue-gray hyperpigmentation exhibiting whorls and swirls similar to marble, which some compare to Chinese letters, along the Blaschko lines is the typical lesion of incontinentia pigmenti.

Hyperpigmented macules that fuse to cause a reticular pattern, mainly in the axilla and groin, along with pits in the perioral and palmar areas, are typical of Dowling-Degos disease.

Diffuse hyperpigmentation

Diffuse hyperpigmentation is a feature of several endocrine disorders, but it is usually accompanied by other characteristic signs. Hyperpigmentation in Addison's disease is more prominent in areas that may be darker in normal individuals, such as the knees and elbows. Involvement of nipples and mucosal areas is also common. On the other hand, hyperpigmentation in Cushing's disease does not usually present with mucosal hyperpigmentation, and in

Table 26.1 Hyperpigmentation due to genetic factors.

Brown color	Gray-blue color
Lentigines	Nevus of Ota
Multiple lentigines syndrome	Nevus of Ito
Peutz–Jeghers syndrome	Blue nevus
Café-au-lait macules in neurofibromatosis	Diffuse melanocytosis
Bloch–Sulzberger syndrome	Incontinentia pigmenti
Melanotic macules in Albright's syndrome	Naegeli–Franceschetti–Jadassohn syndrome
Acanthosis nigricans, juvenile type	
Xeroderma pigmentosum	
Fanconi's syndrome	
Dyskeratosis congenital	
Familial progressive hyperpigmentation	

iatrogenic Cushing's disease, hyperpigmentation is even more uncommon. Diffuse hyperpigmentation may also be observed in acromegaly and hyperthyroidism.

Macular amyloidosis presents clinically as hyperpigmented plaques with an undulating surface, brownish or blackish in color, with ill-defined borders, usually located in the interscapular region, which may be associated or coexist with notalgia paresthetica. In amyloid lichen, there are slightly pruritic coalescing papules that are either hyperpigmented or the same color of the skin, usually located in the legs or arms.

Diffuse hyperpigmentation can also be secondary to other systemic disorders, including hemochromatosis, cirrhosis, cardiac failure, arthritis, diabetes mellitus, systemic sclerosis, systemic lupus erythematosus, and dermatomyositis. One should also have in mind that any erythroderma may heal, leaving diffuse hyperpigmentation.

A long list of medications interact with the melanin system and may cause diffuse hyperpigmentation with a variety of mechanisms. These include, but are not limited to, oral contraceptives, psoralens, phenytoin, phenothiazines, antimalarials, tetracyclines, and several cancer chemotherapy agents. Drug-induced hyperpigmentation should not be viewed as diffuse only; in many cases, the same agents might cause localized darkening of the skin.

HISTORY

History offers invaluable insight into all hyperpigmentation disorders, but may be the only tool to help diagnose secondary localized hyperpigmentation. A history of pregnancy, use of oral contraceptives, endocrine disorders, and hormonal treatments are commonly associated with melasma. Riehl melanosis, erythrose pigmentaire peribuccale of Brocq, and phototoxic hyperpigmentation are common in patients using cosmetics with photosensitizing ingredients, such as coumarins. Industrial exposure to oils or petrolatum might also be the cause

Table 26.2 Acquired hyperpigmentation disorders.

Brown color	Gray-blue color
Metabolic	
Liver disease (hepatolenticular degeneration, biliary cirrhosis)	Hemochromatosis
Porphyria (porphyria cutanea tarda and variegata, erythropoietic [congenital] porphyria)	
Endocrine	
ACTH and MSH-producing pituitary and other tumors	
Addison's disease	
ACTH therapy	
Pregnancy	
Contraceptives and estrogens	
Melasma (chloasma)	
Chemical	
Arsenic	Minocycline
Busulfan, bleomycin, cyclophosphamide	Fixed drug eruptions (barbiturates, phenolphthalein)
Adriamycin	Phenothiazines
Psoralens	Chlorpromazine
Berloque dermatitis	
Phytophotodermatitis	
Physical	
UV light, ionizing radiation, trauma	
Nutritional	
Kwashiorkor	
Pellagra	
Sprue	
Vitamin B12 deficiency	
Postinflammatory	
Eczema	Pinta
Lichen planus	Erythema dyschromicum perstans
Lupus erythematosus	
Lichen and macular amyloidosis	
Systemic sclerosis	
Morphea	
Tumors	
Melanoma	Metastatic melanoma
Acanthosis nigricans with adenocarcinoma	
Malignant tumors	

Note: ACTH, adrenocorticotrophic hormone; MSH, melanocyte-stimulating hormone.

of hyperpigmentation. A history of pruritic dermatoses might help identify hyperpigmentation in nonexposed skin. A history of sitting next to a fireplace, or using electric heating pads or blankets, will confirm erythema ab igne hyperpigmentation lesions. Hyperpigmented lesions in adults that can be associated with a history of bullae

lesions in childhood along the Blascho lines are typical of incontinentia pigmenti. Acanthosis nigricans is often related to endocrine disorders, such as obesity, insulin resistance, type II diabetes mellitus, and polycystic ovary syndrome.

HISTOPATHOLOGY

Histopathology can identify the level of melanin deposition, but similar findings are observed in several hyperpigmentation disorders. Histopathology in melasma shows increased melanin in the basal layer keratinocytes and incontinence of pigment. In secondary hyperpigmentation,

histopathology shows deposition of melanin in dermal macrophages. Epidermal atrophy might accompany the incontinence of pigment in erythema ab igne and lupus erythematosus. In postinflammatory hyperpigmentation, a histology of active inflammatory lesions, if they coexist with hyperpigmentation, may be of paramount importance in getting a diagnosis.

WOOD'S LAMP EXAMINATION

Wood's lamp examination (340–400 nm) highlights the difference in pigmentation of the affected skin. Even though findings are similar in all epidermal melanin

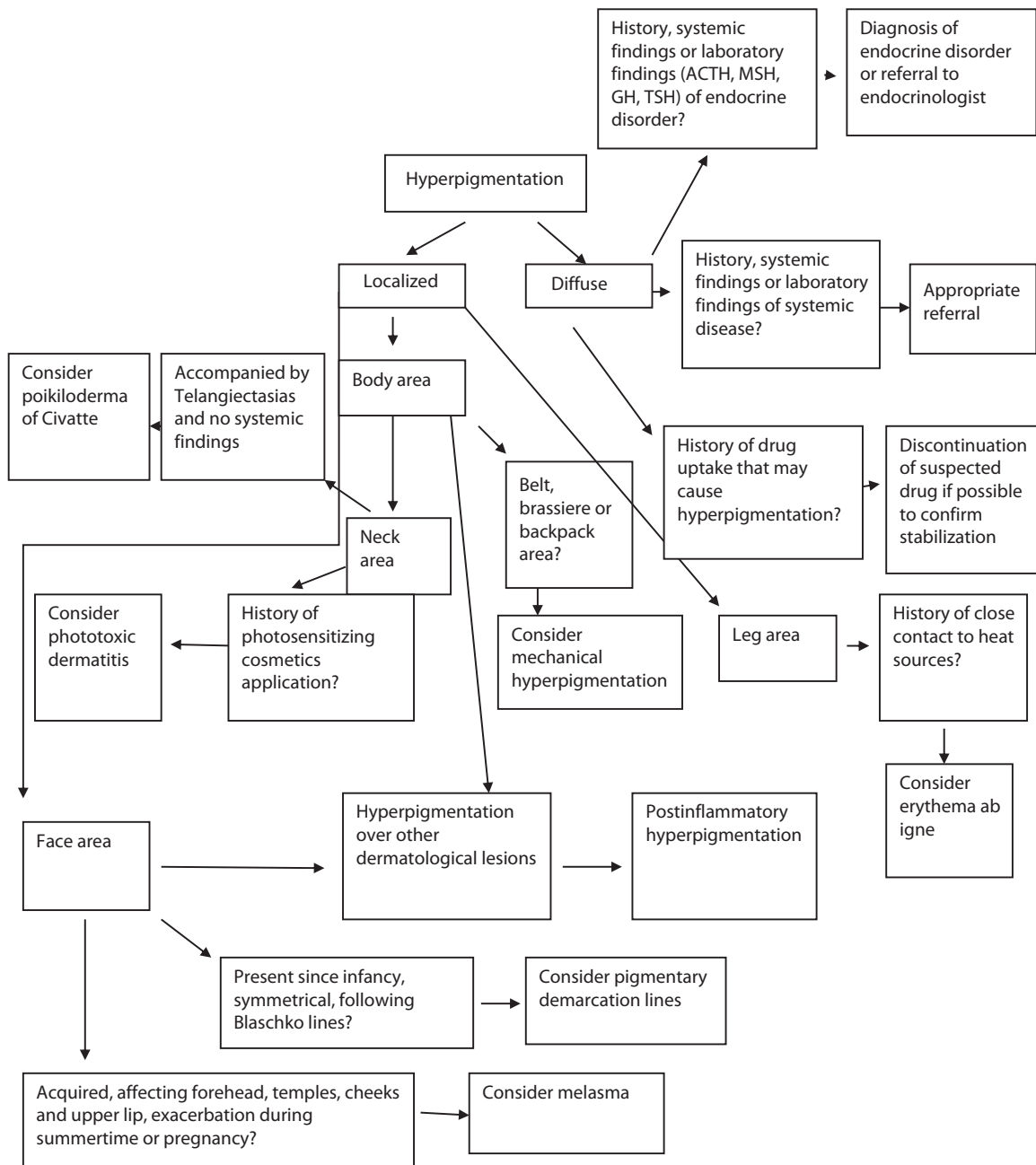


Figure 26.1 Diagnostic algorithm. ACTH, adrenocorticotrophic hormone; GH, growth hormone; MSH, melanocyte-stimulating hormone; TSH, thyroid-stimulating hormone.

deposition disorders and all dermal deposition disorders, discerning the depth of melanin deposition is important for establishing therapeutic options and outcomes. Wood's light enhances the color contrast between hyperpigmented areas and normal skin in epidermal hyperpigmentation. Dermal-type hyperpigmentation presents as ashen or bluish-gray and exhibits no accentuation of color contrast under Wood's light. In the mixed-type hyperpigmentation, the lesion is usually dark brown, and Wood's light enhances the color contrast in some areas, whereas others show no change.⁸ Hyperpigmentation (usually melasma) that is more intensely seen under Wood's light examination responds better to topical treatments.

DERMOSCOPY

Dermoscopy of hyperpigmentation disorders could help avoid a biopsy in cosmetically critical areas such as the face. The color intensity of melanin and the regularity of the pigment network reveal the density and location of melanin. It presents with a dark brown color and well-defined network when located in the stratum corneum, shades of light brown and irregularity of the network when located in the lower layers of the epidermis, and blue or bluish-gray when located in the dermis. Dermoscopy of melasma shows diffuse reticular pigmentation, follicular sparing and sparing of acrosyringium, and uniform globules of pigmentation. In ochronosis, there is no follicular sparing, and amorphous brown areas with arciform structures are observed.⁹ Pseudonetworks, gray dots or granules, liquefaction of basal cells, and incontinence of pigment were the most distinctive characteristics in a case series of Riehl's melanosis.¹⁰ The most common dermoscopic finding of primary cutaneous amyloidosis has been reported to be a central hub, which could be either white or brown, surrounded by various configurations of pigmentation.¹¹

CONCLUSIONS

Even though history and clinical examination will determine a diagnosis in most cases of hyperpigmentation disorders, dermoscopy, histology, and Wood's lamp examination can confirm the diagnosis and provide useful insight on the depth of melanin deposition and,

consequently, on treatment options and prognosis. A diagnostic algorithm considering the most common hyperpigmentation diagnoses is provided in Figure 26.1.

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Differential diagnoses of circumscribed and diffuse hyperpigmentation

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INTRODUCTION

The assessment of a hyperpigmented lesion or disorder, the differential diagnosis, and consequently, the diagnosis compose a challenging procedure. Giving answers to the appropriate questions in sequence diminishes the differential diagnosis to a small and thus manageable number of possible diagnoses and brings the physician closer to the right one.

The *first question* is quite easy to answer. Is the hyperpigmentation disorder circumscribed or diffuse? If the physician distinguishes the lesion from the surrounding healthy skin, then a circumscribed lesion is recognized. Otherwise, the disorder is characterized as diffuse.

The inevitably posed *second question* is whether the lesion was *present at birth*. If it is congenital, and therefore apparent from the first day of life, the differential diagnosis is rather easy. If it was not present at birth and appeared during infancy, childhood, adolescence, or adulthood, it is usually classified as acquired. The hyperpigmented lesions that exist at birth but are not clinically apparent are classified by scientific literature as either acquired or congenital. This group of lesions includes inherited conditions, hamartomas, or some types of nevi, which become evident later in life. They are attributed to congenital disorders after the diagnosis is made, and therefore are retrospectively considered congenital.

The *third question* seeks information about the clinical appearance of the hyperpigmented lesion. What does it look like? The *morphology* is determined by numerous features:

1. Distribution and location. Does the lesion exhibit a predilection for a specific area? Does it involve the mucosal surfaces, the nails, or the hair? Is it generalized?
2. Color.¹ The color perceived by vision depends on the basic *hue*, which is produced by the selective absorption of one or more wavelengths of light by the chromophore. When the chromophore is confined in the fine, translucent epidermis, it absorbs the shorter wavelengths of the white light and allows us to see the complementary colors. Therefore, melanin is brown, but just the epidermal melanin, as the *depth* at which the pigment is located or has been deposited also determines the color. If exactly the same pigment, e.g., melanin, moves into dermis, then the hue perceived by our eye is bluish. This is the optical result of the *Tyndall phenomenon*, according to which the shorter wavelengths (e.g., blue) are scattered and the longer ones (e.g., red) bend around the structures and penetrate more deeply. Another determinant

factor of color is *homogeneity*, which corresponds to another quality of colors, the *saturation*. If the hyperpigmented lesion is interrupted or diluted by other components, such as telangiectasia or atrophy, the color is altered. In addition, the hue tends to shift toward the color that is complementary to the surrounding skin (the color contrast phenomenon), if *contrast* is significant. The physician should always consider the patient's *constitutive skin color* during description of pigmented lesions.

3. Infiltration. Is the lesion macular or infiltrated? Are there any papular or nodular components in the macular lesion?
4. Margin. Is it elevated, regular, irregular, rolled, etc.?

The *fourth question* concerns the *structure of a lesion* as it appears underneath the dermoscope. Is the information given by dermoscopy sufficient for the diagnosis? The lesion is described as melanocytic or nonmelanocytic, malignant or benign, having a network, discrete structures, specific vascular pattern, one color or more.

By the *fifth question*, the physician intends to disclose the history. This comprises the patient's medical history and the history of the lesion. The general medical information is always significant. Many disorders develop due to systemic diseases or drugs or exposure to chemical agents. Changes in skin color guide the physician to a more sophisticated differential diagnosis when a systemic disorder is suspected.

If all the previous steps are insufficient to settle a diagnosis, the histopathology gives a definite answer. The aim of an ideally implemented differential diagnosis procedure is to either elucidate the diagnosis during clinical examination or achieve the minimum of possible diagnoses for the histopathologic assessment. Numerous other laboratory tests or imaging techniques can be used to elucidate the diagnosis.

TAKING STEPS TOWARD DIAGNOSIS IN DISORDERS OF COLOR

Step 1: Demarcation

- Circumscribed
- Diffuse

Step 2: Presence at birth

Is the lesion apparent since birth?

- If yes, it is congenital.
- If no, it is acquired.

Step 3: Clinical morphology**Distribution**

- Skin, hair, nails, and mucosal involvement
- Predilection for specific anatomic sites
- Pattern of distribution

Color

- Homogeneity: Homogeneous, mixed, or mottled
- Hue of the lesion: Black, brown, blue, gray, or green
- Lightness: Dark or light

Infiltration

- Flat lesions (macules and patches)
- Infiltrated lesions (papules, plaques, and nodules)
- Lesions with admixed flat and infiltrated components

Border or margin

- Elevation (e.g., raised or flat)
- Shape (e.g., regular, round, irregular, or notched)

Step 4: Dermoscopic features**Dermoscopic structures**

Step 1 in dermoscopy: The structures that are visible by dermoscopy enable the physician to determine if the lesion is melanocytic. The initial part of the procedure is common to all diagnostic algorithms.²

Is it a pigmented melanocytic lesion? Search for pigment network, either typical or atypical, pseudonetwork, aggregating globules, and branched streaks (except blue nevus).

- *If yes, proceed to the second step.*
- *If no, consider a blue nevus: “Homogeneous” steel-blue color (do not forget to differentiate from melanoma and melanoma metastasis).*
- *If it is not a blue nevus, consider a seborrheic keratosis (SK).*
- *If it is not a SK, consider a pigmented basal cell carcinoma (Figure 27.1).*



Figure 27.1 Dermoscopy of pigmented BCC. (Courtesy of M. Kyriazopoulou.)

- *If it is not a pigmented basal cell carcinoma (BCC), consider a vascular lesion (lacunae are visible).*
- *If it is not a vascular lesion, consider a melanocytic lesion for a second time.*

Numerous well-established dermoscopic features³ have been added to the dermatologist's weaponry during recent years and have facilitated the differential diagnoses of lesions that appear similar to naked eye (Table 27.1).

Step 2 in dermoscopy: If the lesion is classified as melanocytic, then move to any of the four well-known algorithms in order to label a lesion as malignant or benign:^{6,7} (1) pattern analysis, (2) ABCD rule (in dermoscopy), (3) seven-point checklist, and (4) Menzies' method.

Table 27.1 Dermoscopic features.

Melanocytic lesions	Nonmelanocytic lesions
Pigment network (typical or atypical) ^a	Basal cell carcinoma ⁵ Leaflike areas
Pseudonetwork	Spoke wheel-like structures
Globules	Blue-gray ovoid nests
Branched streaks	Multiple blue-gray globules
Homogenous blue color	Seborrheic keratosis
Dots	Comedo-like openings
Streaks (radial streaming and pseudopods)	Milia-like cysts
Blotches	Moth-eaten border
Negative network ⁴	Fingerprint-like structures
Structureless areas	Fissures and ridges ^b
Regression	
Blue-white veil	

^a Exceptions: Delicate pigment network also detected in dermatofibroma, supernumerary nipple, and solar lentigo.

^b Fissures and ridges give a brain-like appearance to the lesion. They are usually recognized in SK, but their presence in dermal and congenital melanocytic nevi is also possible.

Table 27.2 Characteristics vascular patterns in pigmented lesions.

Vascular patterns in pigmented lesions	Type of pigmented lesion
Lacunae (violaceous, blue, brown, or black)	Hemangioma, angiokeratoma
Comma-like vessels	Nevus (dermal or compound)
Dotted vessels	Melanoma, Spitz nevus
Glomerular vessels	Melanoma, pigmented Bowen disease
Corkscrew vessels	Melanoma, melanoma metastasis
Hairpin vessels	Seborrheic keratosis
Polymorphous vessels	Melanoma
Arborizing vessels	Pigmented basal cell carcinoma

Vascular patterns in dermoscopy

Each one of the vascular patterns is suggestive or characteristic of a certain type of pigmented lesion (Table 27.2).

Dermoscopy provides a “handheld” solution and interposes a diagnostic step between clinical examination and biopsy. Nevertheless, in some cases the diagnostic value of dermoscopy is limited owing to lack of specific criteria. The physician should put the dermoscope on every lesion, even on those which seem easy to diagnose.

Step 5: History

Medical history

- Treatment: Systemic (e.g., chemotherapeutic agents or hormones) or topical (e.g., hydroquinone or meclor-ethamine) agent
- Exposure to chemical agents: Occupational or accidental (e.g., bismuth, silver, or mercury)
- Systemic disorder: Diagnosed or suspected (e.g., internal malignancy, malnutrition, or endocrine disease)
- Miscellaneous information: Accidents (foreign bodies in the skin), family history (inherited disorders), etc.

History of the lesion

- Etiology: Inflammatory or noninflammatory (i.e., neoplastic, metabolic, or nutritional), inherited or sporadic
- Previous treatment of another skin condition: Laser treatment, peeling, surgical excision, electrodesiccation, cryotherapy, or injection of a pigmented substance (i.e., posttreatment hyperpigmentation and tattoos)
- Course of a disorder: Location at onset, color changes, size alteration, symptoms, or resolution of a primary lesion
- Association with exposure to sun or light (i.e., tanning and possible phototoxicity or photosensitivity reaction)

DESCRIBING COLOR

As mentioned above, a plethora of agents contribute to the color of the skin. The main determinant of skin color is melanin. The type, amount, and distribution of melanin throughout the skin play a significant role. Additional types of chromophores are hemoglobin, collagen, lycopene, carotene, chemicals, and drugs. The spectrum of light striking the skin, its physical factors, and the transparency of the epidermis widely affect the color.

The description of a colored lesion is crucial for diagnostic, educational, investigative, and therapeutic purposes. Differential diagnosis depends on the accuracy of the description, and confusion may arise when a common lexicon does not exist. Recently, an attempt to establish terminology has been proposed (Table 27.3).⁸

Melanin can be detected throughout the skin: in the epidermis (melanocytes and keratinocytes), in the dermoepidermal junctional zone (melanocytic nevi cells), in the dermis (melanin incontinence, melanocytic nevi cells, melanocytic cells of pigmented neoplasms, and melanophages), and in the subcutis (cells of congenital nevi).

Table 27.3 The description of color in skin lesions.

Terms	Definitions
Discoloration	Altered skin color
Hyperchromia	Skin color darker than normal from any cause
Hyperpigmentation	Excessive amounts of melanin caused by any mechanism
Hypermelanosis	Hyperpigmentation pertaining to increased epidermal melanin (<i>Hyper</i> : Origin from Greek <i>υπέρ</i> [<i>hupér</i>], i.e., “over” and <i>μελάνωση</i> [<i>melánosí</i>], i.e., “the state of being or turning dark or black”; <i>melanin</i> : origin from ancient Greek <i>μέλας</i> [<i>mélas</i>], i.e., very dark or black)
Hypermelanocytosis	Increased population density of melanocytes (epidermal, dermal, or both) resulting in hypermelanosis
Dyschromatosis	Combination of hyper- and hypomelanosis (mixed or mottled pattern of pigmentation)
Poikiloderma	Hypermelanosis admixed with hypomelanosis, atrophy, and telangiectasia

The primary lesions that compose many hypertmela-notic entities are described here, clinically and histologically (Table 27.4):

1. *Ephelis* (freckle) is a small, well-circumscribed, round to oval or irregular, light to dark brown macule (1–4 mm in diameter). Ephelides typically appear on sun-exposed surfaces in individuals with fair skin or may associate with syndromes (Figure 27.2a and b).
2. *Lentigo* is a small, well-demarcated, round to oval, light to dark brown macule (3 mm to 2 cm or more). It is usually darker than ephelis and appears either on sun-exposed skin (solar lentigo) or anywhere on the body, including mucous membranes (lentigo simplex).
3. *Café-au-lait macule* (Figure 27.3) is a well-defined, light to dark brown macule or patch (2–20 cm in diameter) that can be localized everywhere on the body, except mucous membranes.
4. *Melanocytic nevus* is a common round to ovoid macule or papule (2–6 mm in diameter usually), light brown (or skin-colored) to blue or black in color, depending on the type.
5. *Dermal melanocytosis* is observed in specific lesions that appear blue or blue-gray and implies the presence of melanin in melanocytes that are confined in the deep dermis.

FEATURES AND CLUES FOR THE DIAGNOSIS: ASSESSMENT OF THE HYPERPIGMENTED LESIONS OR DISORDERS AND DIFFERENTIAL DIAGNOSES

Melanotic and melanocytic lesions comprise the family of hyperpigmented lesions. Nevertheless, *hyperpigmentation* is

Table 27.4 Dermatopathology of primary hypermelanotic lesions.

Primary lesion	Histology ^a
Ephelis (freckle)	- Increased melanin in basal layer of the epidermis - Normal or decreased number of more productive melanocytes - Absence of elongated rete ridges and melanocytic foci - Long and rod-shaped melanosomes (ultrastructural feature)
Lentigo	- Increased number of melanocytes and excessive melanin - Elongated rete ridges (varying in mucosal lentiginos) - Absence of melanocytic nests - Either solar elastosis (solar lentigo) or not (lentigo simplex) - Melanophages and mild inflammatory infiltrate in upper dermis - Acanthosis in mucosal lentiginos - Macromelanosomes (ultrastructural finding)
Café-au-lait macule (CALM)	- Increase of melanin in the basal layer - Normal density of melanocytes in otherwise healthy individuals (<i>but</i> higher in CALM and healthy skin of patients with neurofibromatosis) - No elongation of rete ridges, no melanocyte nests - Macromelanosomes
Melanocytic nevus	Acquired Melanocytes localized - In the dermal-epidermal junction and upper dermis, arranged in clusters or nests (Type A or epithelioid cells: large nucleus, abundant amphophilic cytoplasm, and mitotic activity possible) - In the middermis, mainly arranged in bands and interlaced cords (Type B or lymphocyte-like cells: smaller, dark nucleus, and less cytoplasm) - In the deep dermis, arranged in nests (Type C or neuroid cells: spindle-shaped cells with sparse melanin, cessation of proliferation, and maturation of nevus cells) Nevi histopathologically classified as - Junctional (Type A cells) - Compound (Type A and B cells mainly, Type C occasionally) - Intradermal (Type C cells) The clinical appearance corresponds to the histology, so the same terms are used to describe a lesion clinically Congenital Melanocytes confined deeply in the dermis (resembling the compound or intradermal acquired nevus pattern) and in subcutaneous tissues and structures (i.e., fat septa and fascia) Cells infiltrate the adnexal structures, nerves, and vascular walls
Dermal melanocytosis	- Normal epidermis - Spindle-shaped dendritic melanocytes in the deep dermis with or without additional pathologic findings (e.g., melanophages and sclerosis)

frequently used as a synonym of *hyperchromia* in scientific literature. The initial assessment of a patient and the subsequent differential diagnosis should always be based on the assumption that the origin of the discoloration is not known. Therefore, a hyperpigmented lesion or disorder must be distinguished from nonpigmented (nonmelanotic) hyperchromatic and hyperpigmented lesions as well. It is clear that the differential diagnosis of hyperpigmentation would be incomplete if the nonmelanotic lesions were not included.

A disorder consisting of or containing ephelides, café-au-lait macules, lentiginos, nevi, or dermal melanocytosis is a hyperpigmented one by definition. The origin of the chromophore is not always conspicuously melanin. Histology, if it is performed, provides a definite answer.

Other laboratory tests or imaging studies elucidate the diagnosis in many cases. The chromophore is then retrospectively determined, and histopathological examination is not required for confirmation of the diagnosis.

The lesions of hyperchromia, either circumscribed or diffuse, represent or are attributed to congenital or acquired conditions. Therefore, four basic groups are derived: congenital circumscribed (Table 27.5), acquired circumscribed (Table 27.6), congenital diffuse (Table 27.7), and acquired diffuse (Table 27.8) disorders. Some of them become apparent very early in life. In such cases, the history may be inaccurate due to blurred memories and emotional distress of parents. The physician is advised to include both congenital and acquired conditions in the differential diagnosis and



(a)



(b)

Figure 27.2 (a and b) Crowe sign: the presence of axillary freckling in patients with neurofibromatosis type 1. (Courtesy of E. Rallis.)



Figure 27.3 Café-au-lait macules in a patient with neurofibromatosis type 1. (Courtesy of E. Rallis.)

perform a thorough examination of the patient. Total body physical examination may reveal special features and divert the diagnostic thought from one perspective to another. For example, certain skeletal deformities or abnormalities of the genitalia suggest specific disorders, and potential failure to detect them results in a “disoriented” differential diagnosis. If a clinical entity is suspected, special laboratory tests (e.g., blood, urine tests, polymerase chain reaction [PCR], and KOH examination) or imaging studies should be performed.

Acral pigmentation is a relatively small subgroup of hyperchromias (Table 27.9) that includes distinctive disorders such as reticulate acropigmentation of Kitamura, as well as lesions that need to undergo further investigation, such as volar macules (Table 27.10). Poikilodermas (Table 27.11) exhibit a wide spectrum of heterogeneous conditions; this category encompasses inherited or acquired disorders, associated with systemic diseases, syndromes, habits, or treatments. Acquired poikilodermatous diseases may appear rather confusing because hyperpigmentation is intermingled with other cutaneous elements. Nevertheless, when poikiloderma is recognized, the cause is disclosed by the typical features of the primary condition.

Table 27.5 Congenital circumscribed.

Lesions/disorders		Features and clues	Assessments/DDs
Lentigines	LEOPARD syndrome ^{10,11}	- AD - Lentigines present at birth or appear in childhood <i>Clue:</i> LEOPARD is an acronym	- CE (ocular hypertelorism, retardation of growth, deafness, and abnormalities of the genitalia) - Imaging and LS (electrocardiogram [ECG] abnormalities and pulmonary stenosis) <i>DD:</i> All the congenital lentiginous syndromes or those developing during infancy
	Peutz–Jeghers syndrome ^{12,13}	- AD - Lentigines present at birth or appear in childhood <i>Clues:</i> Lentigines on buccal mucosa, gums, and hard palate are usually permanent - Lentigines on the central face, hands, and feet fade during adulthood	- CE - Endoscopic studies (gastrointestinal hamartomatous polyps; always involving the jejunum) <i>DD:</i> All the congenital lentiginous syndromes or those developing during infancy, especially Laugier–Hunziker syndrome
	Centrofacial neurodysraphic lentiginosis ^{14,15}	- AD disorder (extremely rare) - Lentigines restricted to a centrofacial band <i>Clue:</i> High-arched palate	- CE (mental retardation observed later in life) - Imaging techniques (central nervous system [CNS] defects and spina bifida) and LS (epilepsy) <i>DD:</i> All the congenital lentiginous syndromes or those developing during infancy
	Carney complex ¹⁶	- AD disorder - Conjunctival lentigines, <i>but not</i> buccal - Blue nevi <i>Clue:</i> Mucocutaneous myxomas (external ear and eyelid)	- CE (skin manifestations) - Imaging techniques (atrial myxomas, psammomatous melanotic schwannomas, and pigmented nodular adrenocortical hyperplasia) <i>DD:</i> All the congenital lentiginous syndromes or those developing during infancy
	Bannayan–Riley–Ruvalcaba syndrome	AD disorder (genetic basis, as in Carney complex) <i>Clue:</i> Genital lentigines	- CE (congenital lipomatosis, hemangiomas, and macrocephalia) - Endoscopy (gastrointestinal polyps) <i>DD:</i> As above
	Lentigo simplex	- Sporadic - Rare as congenital - Solitary	- CE - Dermoscopy <i>DDs</i> - Café-au-lait macule - Congenital nevus
	Speckled lentiginous nevus	This nevus has a lentiginous component often apparent at birth	- CE (darker macules or papules like “speckles” appear later in life) - Dermoscopy
Café-au-lait macules (CALMs)	Neurofibromatosis type 1 (NF1) (Figure 27.4)	- AD (new mutations in 50% of the patients) - CALMs in 85% of the patients <i>Clue:</i> Lesions present at birth - CALMs (50% of the patients) - Intertriginous freckles, i.e., small CALMs (10% of patients)	- Always apply the criteria (at least two must be fulfilled) when NF1 suspected <i>Do not forget to consider</i> the segmental NF1 (mosaicism) <i>DD:</i> The congenital disorders containing CALMs listed here
	Neurofibromatosis type 2 (NF2)	AD disorder <i>Clue:</i> 30% of patients exhibit CALMs	Always apply the criteria if NF2 suspected (at least one needed for the diagnosis) <i>DD:</i> As in NF1
	Tuberous sclerosis (TS) (Figure 27.5)	AD (two responsible genes), <i>but</i> inherited only in 25% of patients <i>Clue:</i> One or more CALMs may be present at birth	Apply the diagnostic criteria if TS suspected <i>DD:</i> Westerhof syndrome (primarily) and the other syndromes displaying CALMs

(Continued)

Table 27.5 (Continued) Congenital circumscribed.

Lesions/disorders	Features and clues	Assessments/DDs
	Westerhof syndrome • Very rare sporadic disorder • CALMs present at birth <i>Clues</i> • Hypopigmented macules in spatial proximity with the CALMs • Twin spotting phenomenon or didymosis provides a possible explanation¹⁷	• CE (growth retardation <i>in utero</i> and during infancy) <i>DD</i>: Tuberous sclerosis (primarily)
	McCune–Albright syndrome • Mosaicism (mutation incompatible with life, and evident only in mosaics) <i>Clue</i>: Irregular border reminiscent of “coast of Maine”; mosaicism pattern Type 1b (Blaschko lines in broad bands), restricted unilaterally	• CE (precocious puberty in girls) • Laboratory tests (hyperthyroidism and Cushing syndrome) • Imaging techniques (osseous defects: bony overgrowth, primary union of the epiphyses, deformities, and fractures) • Endocrine disorders <i>DD</i>: Neurofibromatosis (primarily) and other CALM-demonstrating syndromes
	Watson syndrome • AD (allelic to NF1) • Intertriginous freckling	• CE (Lisch nodules, mental retardation, and short stature) • Imaging studies (neurofibromas and pulmonic valve stenosis) <i>DDs</i> • Neurofibromatosis • Noonan syndrome
	Noonan syndrome¹⁸ • AD (allelic to NF1) • Intertriginous freckling <i>Clues</i> • Ulerythema ophryogenes • Woolly hair • Primary lymphedema	• CE (short stature and pterygium colli) • Imaging studies (pulmonic valve stenosis and skeletal defects) <i>DDs</i> • Neurofibromatosis • Watson syndrome
	Silver–Russel syndrome¹⁹ • X-linked recessive (AR gene and dominant gene produced by germline translocation mutation in father also described²⁰) • Multiple CALMs	• Clinical examination (low birth weight, short stature, macrocephaly, clinodactyly, and hemihypertrophy) <i>DD</i>: CALM-associated syndromes
	Café-au-lait macules • Sporadic • Occasionally present at birth <i>Clue</i>: 1–5 CALMs in 10% of normal population	• Clinical diagnosis (necessity for DD may arise in case of multiple CALMs)
Dermal melanocytosis (blue-gray color)	Nevus of Ota • In most cases, present at birth • Asians and females predominantly affected • Ipsilateral blue-gray lesion localized in the area supplied by first and second branches of trigeminal nerve (upper cheek, upper lip, palate, and buccal mucosa) <i>Clue</i>: Discoloration of sclera	• CE (ipsilateral sensorineural deafness) <i>DD</i>: Nevus of Hori
	Nevus of Ito • Asians predominantly affected • Blue-gray lesion typically distributed in shoulder region <i>Clue</i>: Ota analogue lesion on the body	• CE • Histology <i>DD</i>: Becker nevus

(Continued)

Table 27.5 (Continued) Congenital circumscribed.

Lesions/disorders		Features and clues	Assessments/DDs
	Mongolian spot (Figure 27.6)	- Observed in up to 90% of Asian, black, and Hispanic newborns - Blue-gray hyperpigmentation observed, usually in sacral area <i>Clue:</i> Ectopic lesions reported	CE <i>DD:</i> Lysosomal storage diseases (see congenital diffuse disorders)
	Dermal melanocyte hamartoma	Blue-gray macules displaying tendency to coalesce and form mottled patch <i>Clue:</i> Dermatomal distribution	- CE - Histology
Melanocytic nevi	Congenital melanocytic nevi (Figure 27.7)	- Dark brown macules 3 subtypes (diameter estimated in adults) - Small (<1.5 cm) - Medium sized (1.5–20 cm) - Large/giant (>20 cm) (Giant nevi evaluation in newborn: >9 cm on scalp and >6 cm on the body) <i>Clues</i> - Small nevi present in 1% of newborns - Large/giant nevi reflect mosaicism (Type 4)	- CE and dermoscopy: 4.5%–12% overall lifetime risk for CNS or cutaneous melanoma in large nevi - Imaging studies: Detection of neurocutaneous melanosis in individuals with satellite lesions or giant nevi with axial location (increased intracranial pressure and MRI findings), hypoplasia of limbs
	Speckled lentiginous nevus (see also lentigines)	<i>Clues</i> - Combination of lentigo and darker spots (junctional nevi, compound nevi, and blue nevi) - Spitzoid components (agminate Spitz nevus)	CE <i>DD:</i> Partial unilateral lentiginosis
Didymoses (twin spotting phenomenon)	Phacomatoses	Phacomastosis pigmentovascularis - Type IIa/b (cesioflammea): Dermal melanocytosis <i>and</i> port-wine stain (PWS) malformation - Type IIIa/b: Speckled nevus <i>and</i> PWS - Type IVa/b: Variant combinations of Types II and III - Type V: Dermal melanocytosis <i>and</i> cutis marmorata telangiectatica congenita <i>Clue:</i> Nonallelic didymoses (clinically “paired” areas, genetically different)	- Clinical image (hypermelanosis–vascular abnormality in spatial proximity) - Imaging studies (PWS)

(Continued)

Table 27.5 (Continued) Congenital circumscribed.

Lesions/disorders		Features and clues	Assessments/DDs
Miscellaneous	Pigmentary demarcation lines (Futcher's or Voigt's lines)	- They correspond to the border between darker dorsal and more slightly pigmented ventral surfaces (no histologic differentiation) - Location: Anterolateral surface of upper arm, posteromedial surface of thigh, middle chest area, and spinal area <i>Clue:</i> Present in everyone, but visible in dark-skinned individuals	- CE <i>DDs</i> - Linea nigra in pregnant women - Postinflammatory hyperpigmentation - Linear and whorled nevoid hypermelanosis
	Supernumerary nipples (accessory nipples)	Localization: Along embryonic milk lines (hypermelanotic, connecting anterior axillary fold with upper medial thigh surface) <i>Clue:</i> Ectopic mammary tissue often exhibited (responsive to hormonal changes)	- CE and dermoscopy (dermoscopic image resembles dermatofibroma, but clinically does not demonstrate the "dimple sign")²¹ - Imaging studies (abnormalities of urinary tract and kidneys possible²²) <i>DDs</i> - Dermatofibroma - Leiomyoma - Dermal nevus
	Transient neonatal pustular melanosis	- Neonatal subcorneal neutrophilic vesicles (first phase); rupture produces slight hyperpigmentation and scale (second phase) - Progression to third phase with more prominent and persistent postinflammatory hyperpigmented macules <i>Clues</i> - Third phase apparent at birth in the case of intrauterine initial phase 0.5% (Caucasians) to 5% (African American) of full-term newborns affected	- CE (typical distribution: forehead, nape, chin, lower back, buttocks, anterior lower legs; rapid resolution) - Laboratory tests (absence of pathogen in vesicle content) <i>DDs</i> - Miliaria (crystallina and rubra) - Erythema toxicum neonatorum - Neonatal bullous impetigo - Neonatal candidiasis - Neonatal herpetic infection

Abbreviations: AD = Autosomal dominant; AR = autosomal recessive; CE = clinical examination; DD = differential diagnosis; LS = laboratory studies.

Table 27.6 Acquired circumscribed.

Lesions/disorders		Features and clues	Assessments/DDs
Ephelides	Ephelides (not associated with syndromes)	- AD gene (possibly) - Appear in childhood (primarily seen in red-haired and fair-skinned individuals²³) <i>Clues</i> - Localization on sun-exposed skin only - Tendency to wax (summer) and wane (winter) - Increase in number during childhood, fading in adulthood	- CE - Dermoscopy (no pigment network) <i>DDs</i> - Lentigines - Nevi
	Ephelides as component of syndromes	- Xeroderma pigmentosum (XP) - Progeria - Moynahan syndrome	CE XP and progeria described in poikilodermas
Lentigines	Lentigo simplex	(See “Describing Color” section and Table 27.4, hypermelanosis) - Light to dark brown macule (3 mm to 2 cm or larger) - Located on skin and mucosal areas - Nails: Melanonychia striata (melanoma must be excluded) <i>Clue:</i> Appear everywhere on skin or mucosal surfaces	- Clinical picture - Dermoscopy (delicate and regular pigment network in dermoscopy) <i>DDs</i> - Ephelis - Nevus
	Labial melanotic macule (Figure 27.8)	- Solitary lesion on lower lip - Young Caucasian women predominantly affected	- CE - Dermoscopy - Benign course <i>DD:</i> Venous lake
	Oral melanotic macules	Appear during adulthood (fifth decade of life) <i>Clue:</i> Observed everywhere in the oral cavity, especially on vermilion border	- CE - Dermoscopy - Melanoma surveillance²⁴ 30% of oral melanomas in Caucasians and 60% in Japanese derive from oral melanosis - Dermoscopy (if feasible): Heterogeneity of color blotches, blue-white areas, peppering, regression, irregular-jagged borders favor melanoma diagnosis - Sites of predilection: Hard palate, maxillary alveolus - Age: Over 60 years <i>DDs</i> - Amalgam tattoo - Smoking-associated melanosis - Melanoma
	Anogenital lentiginosis ²⁵	- Adult onset - Benign disorder with unclear pathogenesis <i>Clue:</i> Usually affected sites are labia minora in women and both the glans penis and penile shaft in men	- CE - Dermoscopy (check for signs of atypia or suspicious changes, in case of an uncertain initial diagnosis) - Histology (if you are in doubt, excise it) <i>DDs</i> - Genital nevi - Genital melanoma

(Continued)

Table 27.6 (Continued) Acquired circumscribed.

Lesions/disorders		Features and clues	Assessments/DDs
	Solar lentigo	• Light to dark brown macule (3 mm to 2 cm or larger) • Darker than ephelis <i>Clue:</i> Restricted on sun-exposed areas by definition	• CE • Dermoscopy (homogeneous brown pigment network or pseudonetwork on the face, fingerprint-like structures, irregular margin) <i>DDs</i> • Seborrheic keratosis • Lentigo simplex • Acquired nevus • Lentigo maligna
	Ink-spot lentigo	Black solar lentigo with reticular appearance <i>Clues</i> • On sun-exposed areas only (usually upper back) • Usually smaller than typical solar lentigo (<5 mm)	• CE • Dermoscopy (intensely pigmented, reticulated, broken network) • Histology (if clear-cut diagnosis is difficult, perform biopsy) <i>DD:</i> Melanoma
	Becker nevus (Figure 27.9a and b)	• Hamartoma of ectodermal and mesodermal tissue that becomes apparent during puberty and after sun exposure • Unilateral (shoulder and chest usually) <i>Clue:</i> Hypertrichosis	• CE (ipsilateral musculoskeletal abnormalities possible) • Imaging studies (<i>and if a palpable mass is suspected</i>, detection of possible smooth muscle hamartoma) <i>DDs</i> • Congenital melanocytic nevus • Neurofibromatosis • Nevus of Ito
	Psoralen–ultraviolet A (PUVA) lentigo	• Dark stellate lesion <i>Clue:</i> Usually associated with long-term therapy and high cumulative doses	• CE • History
	Generalized lentiginosis	• Onset during infancy • Sporadic <i>Clue:</i> Lesions tend to appear in groups irregularly	• CE • Clinical course <i>DD:</i> Check for signs and features of acquired lentiginous syndromes and conditions
	Partial unilateral lentiginosis (PUL) ²⁶	• Lentigines appear in clusters restricted to one side of the body (segmental or dermatomal arrangement)	• CE (central nervous system [CNS] abnormalities, e.g., seizures and mental retardation) • Imaging studies (intracranial vascular malformations) • Dermoscopy (lentigines in normal-appearing skin) <i>DD:</i> Speckled and lentiginous nevus (nevi within a macular area)
	Inherited patterned lentiginosis ²⁷	• Generalized lentiginosis in black individuals • AD gene speculated	• Familial occurrence • CE (distribution on face, lips, extremities, palms, soles, and buttocks)

(Continued)

Table 27.6 (Continued) Acquired circumscribed.

Lesions/disorders	Features and clues	Assessments/DDs
	Eruptive lentiginosis ^{28,29}	<i>Clue:</i> Absence of mucosal lesions - Affects individuals in adolescence or early adulthood - Large numbers of lentigines appear in a short period of time (months to a few years) <i>DDs</i> - Dermatosis papulosa nigra - Exogenous ochronosis - Clinical image and characteristic course <i>DDs</i> - Arterial dissections and lentiginosis - Cronkhite–Canada lentiginosis (the rest of acquired lentiginoses should be included)
	Cronkhite–Canada lentiginosis	- Adult onset - Systemic etiology is speculated (e.g., nutritional and infectious) - Large lentigines (up to 10 cm) on the body, face, and extremities <i>Clues</i> - Mucosal surfaces spared - Nail dystrophy, alopecia <i>DDs</i> - CE (diarrhea, weight loss, and abdominal pain) - Endoscopic procedures (gastrointestinal [GI] polyps) - Eruptive lentiginosis - Laugier–Hunziker syndrome^{30,31}
	Laugier–Hunziker syndrome ^{30,31}	- Adult onset - Lentigines on lips and oral mucosa <i>Clues</i> - Melanonychia striata (multiple-nails disease) - Genital and conjunctival lentigines <i>DDs</i> - History - CE - Dermoscopy (always <i>exclude</i> the one-nail involvement of melanoma) - Peutz–Jeghers syndrome (different age of onset) - Cronkhite–Canada lentiginosis
	Arterial dissections and lentiginosis ³²	- Onset during childhood - A few familial cases reported <i>Clues</i> - Lentigines on lower legs <i>DDs</i> - Family history (sudden deaths) - CE (neurologic disorders, e.g., hemiparesis and Horner syndrome) - Duplex sonography, MRI (arterial dissections, cystic medial necrosis of the aorta, and carotid loops) <i>DD:</i> Eruptive lentiginosis
CALMs	Ataxia–telangiectasia syndrome	Table 27.11 (poikilodermas)
Dermal melanocytosis	Nevus of Hori	- Asian women in fourth decade of life or older predominantly affected - Bilateral blue-gray malar patches (occasionally on temporal area and upper eyelid) <i>Clue:</i> Mucosal surfaces spared <i>DDs</i> - CE - Histology - Melasma - Exogenous ochronosis - Postinflammatory hyperpigmentation (PIH) - Nevus of Ota
Tumors	Seborrheic keratosis (SK)	- Benign warty lesion (skin-colored, brown, black) usually seen in elderly people <i>Clue:</i> “Stuck-on” appearance <i>DDs</i> - CE - Dermoscopy (Figure 27.10) - Histology (useful in cases of irritated SK; besides typical features, abundant melanin in basal layer or throughout epidermis is observed) - Melanoma - Epidermal nevus - Condyloma acuminatum - Acquired nevus - Solar lentigo

(Continued)

Table 27.6 (Continued) Acquired circumscribed.

Lesions/disorders		Features and clues	Assessments/DDs
	Dermatofibroma	Firm papule usually located on extremities <i>Clues</i> • Often at sites of arthropod bites • Multiple lesions associated with lupus erythematosus and immunosuppression	• CE dimple sign (Figure 27.11) • Dermoscopy (fine, delicate pigment network with central white area) • Histology (besides typical features, hyperpigmentation of basal layer and hemosiderin deposition detected) <i>DDs</i> • Melanocytic nevus (dermal nevus or previously traumatized junctional) • Supernumerary nipple
	Angiomas	• Dark, dusky red, purple or black discoloration • Thrombosed hemangiomas and angiokeratomas must be included in DDs of hyperpigmented lesions	• Dermoscopy (lucunar pattern) • CE and history • Histology (if you are not sure, perform excision and biopsy) <i>DDs</i> • Melanoma • Malignant angiomatous tumors
	Pigmented basal cell carcinomas	Often demonstrate flat and nodular component (entirely pigmented lesions rare; melanin and melanocytes found within tumor)	• Dermoscopy (leaflike areas, spoke wheel-like structures, blue-gray ovoid nests, multiple blue-gray globules, and arborizing vessels) (Figure 27.1) • Histology <i>DDs</i> • Melanoma • Hemangioma • Blue nevus
	Pigmented adnexal or other occasionally pigmented tumors	• Diagnosis not always easy (Hyperpigmented forms of • Follicular neoplasms • Sweat gland neoplasms • Dermatofibrosarcoma protuberans (DFSP) • Schwannoma)	• Consider them, if clinical and well-known dermoscopic criteria for other tumors not fulfilled or history of lesion “fits” diagnosis (e.g., DFSP) • Histology gives definite answer
	Acquired nevus	Acquired nevi have a distinctive clinical appearance	Always use dermoscopy to exclude melanoma, and if you are not sure about your clinical diagnosis, proceed to excision and biopsy
	Spitz nevus (pigmented)	• Brown or black papule of the trunk or lower extremities • Observed in young adults	• Dermoscopy (“starburst” pattern usually present) • Histology <i>DDs</i> • Always <i>exclude melanoma</i> (blue-white veil seen in both) • Clark nevus: Globules regularly arranged throughout heavily pigmented lesion (use “tape stripping test” to distinguish them)
	Melanoma (Figure 27.12a and b)	Clinically atypical lesion (morphology, history, and signs)	• Dermoscopy (blotches, negative network, structureless areas, regression blue-white veil, and irregular vessels) (Figure 27.13) • Histology <i>DD: from all pigmented tumors</i>

(Continued)

Table 27.6 (Continued) Acquired circumscribed.

Lesions/disorders		Features and clues	Assessments/DDs
	Cutaneous metastatic melanoma (Figure 27.12a)	Blue to black papules or nodules	- History of primary melanoma - Dermoscopy (helpful, not always reliable; homogenous blue-black or blue-gray color with lack of network) <i>DDs</i> - Blue nevus - Angioma, angiokeratoma - Primary melanoma
Associated with inflammation	PIH (Figure 27.14)	See Chapter 15	PIH very often included in DD of acquired hyperpigmentation
	Erythema dischromicum perstans	See Chapter 6	<i>DDs</i> - Lichen planus pigmentosus - Fixed drug eruption
	Fixed drug eruption (Figure 27.15)	- Preceding inflammatory stage with dusky violet plaques (often eroded) - Brown sharply defined round lesions representing PIH - Antibiotics, antimalarials, and sulfonamides are common causative agents <i>Clue:</i> Reexposure to agent leads to recurrence of disorder at exactly the same site	- History of drug exposure or reexposure - Histology (melanophages rich in melanin) <i>DDs</i> (usually easy to diagnose) - Hemorrhage - Arthropod assault - PIH
	Lichen planus pigmentosus (Figure 27.16)	See Chapter 7 and Table 27.12	
Atrophodermas	Atrophoderma of Pasini–Pierini (erythematous localized scleroderma) (Figure 27.17)	See Chapter 11 Hypermelanosis <i>Clue:</i> “Cliff-drop” sign	<i>DDs</i> - Atrophoderma of Moulin - Atrophy caused by prolonged use of topical corticosteroids
	Atrophoderma of Moulin	- Onset in childhood or later - Hyperchromia and atrophy in plaque–lesion along Blaschko lines on the trunk or extremities - Lack of sclerosis - May reflect mosaicism for autosomal lethal gene <i>Clue:</i> No preceding inflammatory stage	- History - CE - Histology <i>DDs</i> - Segmental morphea - Atrophoderma of Pasini–Pierini - Acrodermatitis chronica atrophicans - CE
Primary cutaneous amyloidosis	Lichen amyloidosis	See Chapter 8	Histology (hyperpigmentation due to melanin incontinence)
			<i>DDs</i> - Lichen planus (and hypertrophic variant) - Lichen simplex chronicus

(Continued)

Table 27.6 (Continued) Acquired circumscribed.

Lesions/disorders		Features and clues	Assessments/DDs
	Macular amyloidosis	See Chapter 8	• CE • Histology (hyperpigmentation due to melanin incontinence) <i>DDs</i> • PIH • Lichen simplex chronicus • Notalgia paresthetica (association speculated)
	Biphasic cutaneous amyloidosis	• Coexistence of aforementioned <i>Clue:</i> If it appears as linear, arrangement along Blaschko lines exhibited	<i>DD:</i> As above (in case of linear lesions, consider other Blaschko-associated disorders)
Mycosis	Tinea nigra	• Observed in tropical climates • Causative pathogen: <i>Hortaea werneckii</i> (brown septa hyphae in stratum corneum) • Solitary patch of hyperchromia with sharp margin on palms, soles, neck, and trunk <i>Clue:</i> Dark pigmentation of advancing periphery	• CE (and dermoscopy³³) • Laboratory tests (KOH examination, culture) <i>DDs</i> • Acquired melanocytic nevus (dermoscopy very helpful) • Hemorrhage (in acral lesions)
Mastocytosis	Solitary mastocytoma	See Chapter 9 • Hypermelanosis may be present	<i>DDs</i> • Spitz nevus • Juvenile xanthogranuloma • Arthropod assault
Miscellaneous	Acquired brachial cutaneous dyschromatosis ^{34,35}	• Predilection for Caucasian middle-aged women • Gray-brown hyperpigmented patches on dorsal surfaces of forearms and arms • Association with antihypertensive drugs (ACE inhibitors) speculated <i>Clues</i> • Geographic margin • Hypopigmented macules admixed (mottled)	• CE • History of preceding prolonged sun exposure <i>DD:</i> PIH
	Tattoos • Decorative • Accidental • Iatrogenic	• Possible introduction into skin after accidental, occupational, or medical-procedural exposure • Blue, brown, or black discoloration usually identified <i>Clue:</i> Blue dye for sentinel lymph node (SLN) biopsy in breast cancer may result in prolonged discoloration ³⁶	• History • Clinical image (color and distribution) • Histology (foreign bodies)

Abbreviations: AD = Autosomal dominant; CE = clinical examination; DD = differential diagnosis.

Table 27.7 Congenital diffuse.

Lesions/disorders		Features and clues	Assessments/DDs
Along Blaschko lines	Epidermal nevus (Figure 27.18)	• Subtle clinical picture displayed at birth • Hyperchromia <i>Clue:</i> Diagnosis provided by evolution of lesion during childhood	• CE and course • Histology (epidermal hyperplasia, hyperkeratosis, acanthosis, papillomatosis, and variable parakeratosis) <i>DDs</i> • Other congenital disorders along Blaschko lines • Nevus sebaceous • Nevoid lesions along Blaschko lines (e.g., porokeratotic eccrine ostial nevus and dermal duct nevus) • Linear lichen planus • X-linked dominant chondrodysplasia punctata • Lichen striatus • Linear lichen planus • SK, verruca vulgaris (in cases of small lesions)
	Linear and whorled nevoid hypermelanosis	• Mosaicism (usually Type 1a) • If apparent at birth, it is slightly pigmented (becomes clearly obvious within the first year of life) <i>Clue:</i> Striking pattern of swirls and whorls	• CE • Imaging studies (cardiac, neurologic, and skeletal defects in approximately 25% of patients) • Histology (basal layer hypermelanosis or melanocytosis, and dermal melophages occasionally) <i>DDs</i> • Incontinentia pigmenti (in cases of intrauterine first or second stages) • Epidermal nevus
	Incontinentia pigmenti ³⁷ (Figure 27.19)	• X-linked dominant (97% of patients are women) • Men: Seen as mosaicism or in Klinefelter syndrome • 4 stages: (1) Inflammatory lesions, (2) hyperkeratotic–verrucous lesions, (3) gray-brown or gray-blue hyperpigmentation, and (4) atrophic, hypopigmented lesions <i>Clues</i> • Third stage may be apparent at birth, if first 2 stages occur <i>in utero</i> • Stages may overlap • “Chinese letter”–resembling pattern	• CE laboratory and imaging studies (central nervous system [CNS], ocular, and dental abnormalities; hematological disorders; immunological dysfunction) • Iodine–starch test to detect anhidrotic and atrophic patches <i>DD:</i> Disorders along Blaschko lines
	X-Linked reticulate pigmentary disorder or familial cutaneous amyloidosis or Partington syndrome type II	• X-linked recessive: Congenital only in girls; hyperpigmentation in streaks along Blaschko lines • Delayed onset in boys (fourth month or later); generalized reticulate hyperpigmentation <i>Clues</i> • In girls, fading during adulthood • In boys, short life expectancy due to CNS, gastrointestinal [GI], and urinary tract [UT] abnormalities and severe pulmonary infections	• CE • Imaging studies (detection of abnormalities seen in male patients) <i>DDs</i> • Dyskeratosis congenita • Nageli–Franceschetti–Jadassohn syndrome • Disorders along Blaschko lines

(Continued)

Table 27.7 (Continued) Congenital diffuse.

Lesions/disorders		Features and clues	Assessments/DDs
Dermal melanocytosis or melanin deposit	Lysosomal storage diseases ³⁸	• Extensive blue cutaneous pigmentation with dorsal and ventral distribution • Persistent and/or progressive behavior • Associated with GM1 gangliosidosis type 1 (AR) and Hurler syndrome (AR)	• CE and imaging studies (GM1 gangliosidosis: coarse facies, dysostosis multiplex, neurologic disorders, and organomegaly; Hurler syndrome: coarse facies, mental retardation, organomegaly, skeletal disorders, and corneal clouding) • Diagnostic laboratory tests (GM1 gangliosidosis: urine, leukocytes, and fibroblasts; Hurler syndrome: leukocytes) <i>DD:</i> From Mongolian spots
	Diffuse melanosis cutis ³⁹	• Rare presentation of metastatic melanoma • Blue-gray mucocutaneous hyperpigmentation • Cephalocaudal progression • More intense on sun-exposed areas <i>Clue:</i> Melanuria	• CE (darkening of serum, hair, and peritoneal fluid; expectoration of melanin-containing material) • Histology (melanin in perivascular dermal histiocytes and free melanin in dermal connective tissue, fibroblasts, and epidermal hypermelanosis not always present) <i>DD:</i> Diffuse blue discoloration of skin (see Table 27.15)
Miscellaneous	Dermatopathia pigmentosa reticularis ⁴⁰	• AD disorder (allelic to Naegeli–Franceschetti–Jadassohn syndrome; see Table 27.8) • Hyperpigmentation present at birth or later • Confetti-like macules on trunk and proximal extremities <i>Clue:</i> Adermatoglyphia (not always and not all fingers involved)	• Family history • CE <i>DD:</i> Naegeli–Franceschetti–Jadassohn syndrome
	Familial progressive hyperpigmentation (melanosis universalis hereditaria or universal acquired melanosis) ^{41,42}	• AD disorder • Patches with tendency to coalesce (present at birth) and occupy large body regions <i>Clue:</i> Mucosa and nails affected	• Familial history • CE carbon baby
	Mendes da Costa–van der Valk syndrome	• At birth or early childhood • X-linked recessive inheritance • Reticulate pigmentation with macular atrophy <i>Clue:</i> Red-brown face and extremities	• mental retardation

Abbreviations: AD = Autosomal dominant; AR = autosomal recessive; CE = clinical examination; DD = differential diagnosis.

Table 27.8 Acquired diffuse.

Lesions/disorders	Features and clues	Assessments/DDs
Acanthosis nigricans (Figure 27.20)	- Tiny brown-gray hyperpigmented papules that exhibit a tendency to coalesce and form velvety plaques 7 types recognized - Typical distribution (lateral neck, flexural and intertriginous areas, umbilicus, and nipples) <i>Clue:</i> Papules can be brushed off, revealing villous projections of normal skin	- CE - Imaging studies (internal malignancy) - Histology (hyperkeratosis, papillomatosis, and minimal basal layer hyperpigmentation) <i>DDs</i> - Atopic dirty neck - Confluent and reticulated papillomatosis of Gougerot–Carteaud - Hailey–Hailey disease - Pemphigus vegetans
Confluent and reticulated papillomatosis of Gougerot–Carteaud (Figure 27.21)	- Women and black individuals predominantly affected - Small gray-brown papules of hyperchromia in lacy arrangement typically found on chest, upper back, and nape <i>Clue:</i> Lesions coalesce, forming “dirty” skin appearance	- CE - Histology (hyperkeratosis, papillomatosis resembling SK, epidermal nevus, acanthosis nigricans, and acrochordon) <i>DDs</i> - Acanthosis nigricans - Terra firma-forme dermatosis - Tinea versicolor (KOH examination) - Darier disease
Cantú syndrome	- Onset during childhood or later - AD disorder - Reticulate hyperpigmentation of face, forearms, and feet <i>Clue:</i> Punctuate palmoplantar keratoderma	- Familial history - CE
Dowling–Degos disease ⁴³ (Also consider acantholytic variant of this: Galli–Galli syndrome)	- AD - Adult onset (occasionally earlier in puberty) - Brown macules and papules with tendency to become confluent and form reticulate hypermelanosis; many reports for hidradenitis suppurativa coexistence <i>Clues</i> - Distribution in intertriginous and major flexural areas - Pitted perioral scars, comedo-like lesions on back and neck	- Familial history - CE - Histology (hyperpigmentation due to hypermelanosis and dermal melanophages) <i>DDs</i> - Acanthosis nigricans - Confluent and reticulated papillomatosis of Gougerot–Carteaud - Haber disease
Haber disease	- AD - Onset in adolescence - Reticulate hyperpigmentation (trunk, axillae, and proximal extremities) - Verrucous keratotic papules, comedo-like lesions, pitted scars, and rosacea-like facial erythema <i>Clue</i> - Dowling–Degos-like lesions with facial erythema	- Family history - CE <i>DDs</i> - Dowling–Degos disease - Acanthosis nigricans - Confluent and reticulated papillomatosis of Gougerot–Carteaud

(Continued)

Table 27.8 (Continued) Acquired diffuse.

Lesions/disorders		Features and clues	Assessments/DDs
After sun exposure	Tanning	Sites of exposure affected	- History - CE
	Phytophotodermatitis (Figure 27.22)	- Phototoxic reaction - Exposure to furocoumarins preceding sun exposure - Irregular pigmented lines and streaks forming netlike pattern (melanogenesis) <i>Clue:</i> Primary inflammatory phase (blistering also possible)	- History of contact with plants and juices (e.g., cow parsley, lime, and celery) - CE
	Berloque dermatitis	- Phototoxic reaction - Application of bergamot oil-containing perfume (bergapten or 8-MOP) followed by sun exposure <i>Clue:</i> Striking image of hyperpigmentation (melanogenesis) depicting the sites of application and trickling of the perfume	- History - CE (usually reveals pathogenesis)
Chemical-induced hyperpigmentation	See Table 27.14 Arsenic ingestion	- Arsenic intoxication may be chronic - Latency period of years before clinical expression of the disorders - Mottled hyperpigmentation - Palmoplantar keratoses, BCC, Bowen disease, internal malignancies <i>Clue:</i> Hypopigmentation in “raindrops on a dusty road” pattern	- CE - History (not always suggestive of exposure) <i>DDs</i> - Dyschromatosis universalis hereditaria - Acropigmentation of Kitamura - Dowling–Degos disease - Familial gigantic melanocytosis
Drug-induced hyperpigmentation (Figure 27.23)		See Table 27.14	Medical history (always take detailed information about current, chronic, or discontinued drug treatment)
Dyschromatosis universalis hereditaria		- AD disorder - Onset during childhood - Asians predominantly affected - Widespread hyper- and hypopigmentation <i>Clue:</i> No tendency to fade	<i>DDs</i> - Dyschromic amyloidosis cutis⁴⁴ (differentiated only by histology) - Acropigmentation of Kitamura - Dowling–Degos disease - Familial gigantic melanocytosis
Dyschromic amyloidosis cutis		- Few cases reported - Dotted reticulate hyperpigmentation intermingled with hypopigmented macules - Onset in childhood - Unknown type of inheritance (AD speculated) <i>Clues:</i> No or minimal pruritus	Histology (amyloid deposition in papillary dermis and hypermelanosis) <i>DD:</i> Dyschromatosis universalis hereditaria
Erythema ab igne (Figure 27.24)		- Reticulate erythema leading to a permanent netlike pigmentation in sites of localized, chronic, and cumulative exposure to heat-emitting devices or objects - Poikiloderma - Premalignant skin condition	- Relevant history - CE <i>DD:</i> Livedo reticularis

(Continued)

Table 27.8 (Continued) Acquired diffuse.

Lesions/disorders		Features and clues	Assessments/DDs
Familial gigantic melanocytosis ⁴⁵		- AD gene speculated - Diffuse hyperpigmentation and admixed raindrop-like hypopigmentation - Sun-exposed areas mainly affected	- Familial history - Histology (electron microscopy examination: large melanosomes and large irregular melanocyte nuclei with fragmented chromatin)
		<i>Clue:</i> Sparse axillary and pubic hair, light color of scalp and body hair	<i>DD:</i> from all disorders presenting with "raindrop hypopigmentation," i.e., - Arsenic ingestion - Dyschromatosis universalis hereditaria - Acropigmentation of Kitamura - Dowling–Degos disease
Fanconi's anemia		- Onset during first decade of life - AR disorder (12 gene mutations) - Diffuse hyperpigmentation with CALMs and hypopigmented macules - Squamous cell carcinomas (SCCs) (head and neck) - Increased risk for acute myelogenous leukemia and hepatocellular cancer	- CE (short stature, hypogonadism, and mental retardation) - LS <i>DD:</i> Dyskeratosis congenita
Flagellate pattern - Dermatitis from bleomycin (Figure 27.25) - Mushroom dermatitis		See Chapter 17 Hyperpigmentation (basal layer hypermelanosis and melanin incontinence)	<i>DDs</i> - Dermatomyositis (occasionally flagellate erythema is present) - Adult-onset Still disease
Hemosiderin deposition	Progressive pigmented purpura (Schamberg purpura and variants, i.e., purpura annularis telangiectodes, lichenoid purpuric dermatitis, and eczematid-like purpura) (Figure 27.26)	- Usually located on shins (centripetal spread also occurs) - Red-brown macules of discoloration coalesce and produce patches <i>Clue:</i> Cayenne pepper spots (new petechiae at periphery appear like speckles)	- CE (positive Rumpel–Leede test in the affected areas) - Histology (hemosiderin deposits) <i>DD:</i> Mycosis fungoides (at a primary stage)
	Chronic venous insufficiency (Figure 27.27)	- Discoloration found on medial aspects of calves, ankles, and over perforators - Yellow-brown color <i>Clue:</i> Signs of chronic venous insufficiency may be evident, e.g., lipodermatosclerosis and atrophie blanche	- CE - Histology (hemosiderin deposits and increased melanin due to inflammatory chronic stimulus) <i>DDs</i> - Lichen aureus - Progressive pigmented purpura
Mastocytosis	Urticaria pigmentosa (Figure 27.28)	See Chapter 9 Hyperpigmentation (increased melanin in the epidermis is the real cause, <i>not</i> the observed melanin incontinence)	- CE - History and course - Histology - LS <i>DDs</i> - Multiple leiomyomas - Multiple adnexal tumors - Leukemic infiltrates - Langerhans cell histiocytosis - Lymphomas
Naegeli–Franceschetti–Jadassohn syndrome ⁴⁶		- AD - Onset during infancy or early childhood - Neck and axillae mainly affected with gray-brown reticulate pattern pigmentation (fades in adult life)	- Familial history - CE (palmoplantar keratoderma, hypohidrosis, and yellow enamel) <i>DD:</i> Dermatopathia pigmentosa reticularis

(Continued)

Table 27.8 (Continued) Acquired diffuse.

Lesions/disorders		Features and clues	Assessments/DDs
Ochronosis Alkaptonuria (Figure 27.29a and b)		<i>Clue:</i> Absence of dermatoglyphics - AR - Onset of dermatologic features in childhood (rarely in adolescence) - Deficiency of homogentisic acid oxidase; accumulation of homogentisic acid in tissues and body fluids - Blue to yellow-brown discoloration of ear helices, sclerae, and axillae (face, palms, and soles affected later in life) <i>Clues</i> - Dark urine - Dark cerumen (brown to black)	- History of “brown diapers” - CE (urine turns darker on standing and arthritis) - Laboratory and imaging studies (renal dysfunction and cardiac valve disease) - Histology (typical) <i>DD:</i> From other causes of arthritis and diffuse blue disorders of the skin (see Table 27.15)
Porphyria cutanea tarda		- Types 1 and 2 (acquired and inherited, AD gene mutation) - Increased photosensitivity caused by porphyrin deposition in skin - Bullous lesions on sun-exposed skin, hypertrichosis of temples, and sclerodermoid plaques <i>Clue:</i> Characteristic combination of hyper- and hypopigmentation, scarring and milia	- Relevant history (exposure to alcohol, hormones, contraceptives, and hexachlorobenzene) - CE - Laboratory tests (isocoproporphyrin in the feces) <i>DD:</i> From other porphyrias and sclerodermoid conditions
Postinflammatory hyperpigmentation		See Chapter 15	Postinflammatory hyperpigmentation included in DD of acquired hyperpigmentation
Hutchinson–Gilford progeria syndrome		- AR - Normal at birth, onset during second year - Mottled hyperpigmentation	- CE (short stature, alopecia, and facies) - Laboratory test (cardiovascular disease and insulin resistance) - Imaging studies (thinned cranial bones, open fontanelles, mandibular hypoplasia, and acro-osteolysis)
		<i>Clues</i> - Narrow thorax and short clavicles - Characteristic “progeroid” facies (frontal bossing, micrognathia, thin beaked nose, thin lips, and prominent scalp veins)	<i>DDs</i> - Werner syndrome - Néstor–Guillermo progeria syndrome - Cockayne syndrome - Rothmund–Thomson syndrome - Ataxia–telangiectasia syndrome
Néstor–Guillermo progeria syndrome		- AR - Onset during infancy - Mottled hyperpigmentation - Progeroid facies (frontal bossing absent) <i>Clue:</i> Red swollen phalangeal skin	- CE - Imaging studies (severe acro-osteolysis) <i>DD:</i> Hutchinson–Gilford progeria syndrome
Prurigo pigmentosa		- Young women usually affected (Japan) - Pruritic erythematous papules on trunk and nape leading to reticulated hyperpigmentation after resolution - Intrascapular and sternal distribution (duration of months)	- CE - Histology (dermal melanophages) <i>DD</i> - Lichen planus - Macular amyloidosis
Sclerodermoid conditions	Systemic sclerosis (scleroderma)	Hyperpigmentation in 50% of the patients: Predominantly on face; less frequently on legs, thighs, lower abdomen, axillae, and dorsal surfaces of hands	- CE - Laboratory and imaging studies

(Continued)

Table 27.8 (Continued) Acquired diffuse.

Lesions/disorders		Features and clues	Assessments/DDs
	POEMS syndrome	<i>Clue:</i> Occasionally generalized hyperpigmentation seen - Acronym for - Polyneuropathy - Organomegaly - Endocrine disorders - Monoclonal gammopathy - Skin changes - Diffuse hyperpigmented sclerodermoid lesions and generalized hyperpigmentation observed	- CE (hemangiomas, sclerodactyly, and hypertrichosis) - Laboratory tests (dysglobulinemia) - Imaging studies (hepatosplenomegaly) <i>DD:</i> Scleroderma
Lysosomal storage diseases ³⁸	Niemann–Pick disease	- AR - Diffuse yellowish-brown or ochre discoloration of early onset (infancy) - Extensive and persistent dermal melanocytosis (multiple Mongolian spots) and CALMs <i>Clue:</i> Hyperpigmentation of buccal mucosa	Usually dermatologists have no role in the diagnosis of the disorder
	Gaucher disease	- AR disorder - Melasma-like hyperpigmentation on face, neck, and hands of late onset (adulthood) - Hyperpigmentation on lower legs (sharp lower border, irregular upper)	Usually dermatologists have no role in diagnosis of disorder
Systemic diseases and conditions		See Table 27.13	
Terra firma-forme dermatosis ⁴⁷ (Duncan's dirty dermatosis) (Figure 27.30)		- Dirt-like plaques located on concave surfaces (neck, face, trunk, and ankles) produce this hyperchromia - Delayed keratinocyte maturation suggested as causative factor (keratinocyte buildup with sebum and dirt) <i>Clue:</i> Application of 70% isopropyl alcohol provides both diagnosis and treatment	<i>DDs</i> - Atopic dirty neck - Acanthosis nigricans - Confluent and reticulate papillomatosis of Gougerot–Carteaud - Epidermal nevus - Ichthyosis
Tinea versicolor (Figure 27.31)		See Chapter 10	<i>DDs</i> - Postinflammatory hyperpigmentation - Secondary syphilis
Treponemal infections	Secondary syphilis	Hyperpigmentation (ill-defined dark brown macules) appears after resolution of papulosquamous lesions (pigmented syphilid)	- CE - History (at that stage the diagnosis is usually already known) - Laboratory confirmation
	Pinta	Resolution of pintids produces a mixed and multicolored pattern of hyper- and hypopigmentation (blue, brown, gray, and white macules) <i>Clue:</i> Restriction of pinta in remote areas in Central and South America	<i>DD:</i> Lichenoid drug eruption (resolving) - CE - History of pintids - Laboratory confirmation
Atopic dirty neck ⁴⁸ (hyperpigmentation of the neck in atopics)		Reticulate pattern of hyperpigmentation localized on anterolateral surfaces of neck	- History of atopic dermatitis - CE - Histology (hypermelanosis with mature melanosomes, and melanin in the dermis) <i>DDs</i> - Terra firma-forme dermatosis - Ichthyosis

Abbreviations: AD = Autosomal dominant; AR = autosomal recessive; CE = clinical examination; DD = differential diagnosis; LS = laboratory studies.

Table 27.9 Acral hyperpigmentation.

Disorder	Onset	Distribution	Clinical features—course	Other skin or systemic findings	Histology
Acromelanosis progressiva ⁴⁹	Third month of life (in a Japanese girl)	Dorsum of all fingers and toes (and perianal area)	Blue-black lesions, progressive hypermelanosis	Epileptic seizures	Remarkable basal melanocytosis
Acromelanosis ⁵⁰	At birth (in a Puerto Rican boy)	Periungual areas of the right hand (bluish discoloration of right sclera)	No progression	Seizures and malabsorption syndrome (incidental findings according to authors)	Basal layer melanocytosis
Acropigmentation (“Spitzenpigment”)	At birth or later	Distal phalanges of fingers and toes	Brown hyperpigmentation, gradual fading during childhood or darkening during adolescence	–	Basal layer hypermelanosis, melanophages in upper dermis
Reticulate acropigmentation of Kitamura ^{51,52}	First and second decades of life (AD disorder)	Dorsal surfaces of hands and feet (reticulate pattern)	Hyperpigmented atrophic macules, gradual involvement of other sites	Pits (palms and soles)	Epidermal hypermelanocytosis, epidermal atrophy
Acropigmentation of Dohi (dyschromatosis symmetrica hereditaria)	Early childhood (AD type of inheritance)	Dorsal surfaces of hands, feet, and face	Hyper- and hypopigmented macules, seasonal changes, no atrophy	Neurologic disorders	Hypermelanosis (hyperpigmented macules)
Acromelanosis albo-punctata	Childhood	Dorsal surfaces of hands and feet	Hypopigmented macules on hyperpigmented areas	Papules on legs, pili torti	(Not provided here)
Volar pigmented macules ⁵³	See Table 27.10				

Abbreviation: AD = Autosomal dominant.

Table 27.10 Volar pigmented macules.

Sporadic, idiopathic	Dark-skinned, mostly middle-aged individuals (prevalence ranging from 1.7% in Puerto Ricans to 61% in South African blacks)
Inherited pattern of lentiginosis in blacks	See Table 27.6
Mycosis	• Tinea nigra • Tinea pedis
Postinflammatory hyperpigmentation	Preceding inflammatory lesions in a dark-skinned individual, e.g., phytophotodermatitis
Psoralen–ultraviolet A (PUVA)	History of PUVA treatment
Chemotherapeutic drugs	• 5-Fluorouracil (systemic) • Tegafur • Doxorubicin
Systemic disorders	• Addison disease • AIDS • B12 deficiency⁵⁴
Syndromes	• Laugier–Hunziker syndrome • Peutz–Jeghers syndrome • Carney complex • LEOPARD syndrome • Neurofibromatosis type 1

Table 27.11 Poikilodermas.

Disorders	Acquired/inherited	Features and clues	Assessments/DDs
Ataxia–telangiectasia ⁵⁵	AR gene mutation	- Onset in early childhood (neurologic signs) - Telangiectasia (face, neck, and flexures) - Brown-reddish plaques on face and extremities - Lack of atrophy (incomplete poikiloderma) - Diffuse hyperpigmentation and CALMs in periods of rapid clinical deterioration (inability to walk)	CE and imaging studies (severe pulmonary infections, and malignancies in second decade of life) <i>DD:</i> From other disorders with ataxia (easy to diagnose after the appearance of telangiectasia)
Bloom syndrome	AR gene mutation (Ashkenazi Jews and Japanese affected)	- Onset during infancy - Up to 75% of patients are men - Lack of atrophy (incomplete poikiloderma) - Photosensitivity results in poikiloderma (sun-exposed areas) <i>Clue:</i> Telangiectasia on malar skin is evident from the first month of life	- CE (short stature, polydactyly, and dental abnormalities) - Laboratory and imaging studies (leukemia, lymphoma, and Wilms' tumor) - Short life expectancy <i>DD:</i> Rothmund–Thomson syndrome
Dyskeratosis congenita ^{56–58}	X-linked recessive inheritance (AR and dominant genes have been reported)	- Onset of skin disorders during childhood (hematologic abnormalities appear in second decade of life) - Poikiloderma on chest, neck, and thighs - Reticulate (lacy) hyperpigmentation <i>Clue:</i> Mucosal leukoplakia featuring increased risk for squamous cell carcinomas (SCCs), onychodystrophy	- CE - LS (bone marrow failure, Hodgkin disease, and acute myelogenous leukemia) <i>DD:</i> Fanconi's anemia
Goltz syndrome (focal dermal hypoplasia)	X-linked dominant (extremely rare)	- Apparent at birth as linear ulcerated lesions - Healing produces poikiloderma - Distribution along Blaschko lines - Herniation of fat, local patchy alopecia <i>Clue:</i> Warty peribuccal and perianal papillomas	- CE (lobster claw syndactyly, ocular and dental abnormalities, and cleft palate) - Mental retardation <i>DDs</i> - Incontinentia pigmenti - Nevus lipomatosus - Poikilodermas (with patchy and small lesions)
Gottron syndrome (acrogeria)	AD or AR	- Clinical manifestations at birth - Severe skin atrophy on hands and feet (bruising and prominent veins) <i>Clue</i> - Thick and dystrophic nails - Short phalanges	- CE - Imaging studies (acro-osteolysis) <i>DDs</i> - Reticulate acropigmentation of Kitamura - Kindler syndrome - Hereditary acrokeratotic poikiloderma
Hereditary acro-keratotic poikiloderma (Weary syndrome or Dowling syndrome)	AD gene	- Onset during childhood - Primary inflammatory stage - Atrophic acral skin with warty papules <i>Clue:</i> Acral and flexural involvement	<i>DDs</i> - Kindler syndrome - Gottron syndrome
Hereditary sclerosing poikiloderma (Weary syndrome type 2)	AD gene	- Onset in childhood - Diffuse poikiloderma - Acral sclerosis (keratotic flexural areas) <i>Clue:</i> Absent telangiectasia (incomplete poikiloderma)	- CE - Imaging studies (mandibular dysplasia, acral dysplasia, and cranial defects) <i>DDs</i> - Xeroderma pigmentosum - Arsenic ingestion
Kindler syndrome (epidermolysis bullosa variant)	AR gene mutation	- Congenital blistering - Progressive and extensive poikiloderma - Palmoplantar keratoderma - Nail dystrophy - SCCs (skin and mucosal) <i>Clue:</i> Arachnodactyly	- CE and imaging studies (premature aging; periodontitis; urethral, esophageal, and anal stenosis) <i>DDs</i> - Hereditary acrokeratotic poikiloderma - Acrogeria

(Continued)

Table 27.11 (Continued) Poikilodermas.

Disorders	Acquired/inherited	Features and clues	Assessments/DDs
Poikiloderma with neutropenia (Navajo poikiloderma)	AR gene (first described in Native Americans)	Acral papular exanthem evolving to poikiloderma <i>Clue:</i> Centripetal spread of exanthem	- CE and imaging studies (pachyonychia and pulmonary infections) <i>DDs</i> - Rothmund–Thomson syndrome - Hereditary acrokeratotic poikiloderma - Gottron syndrome
Rothmund–Thomson syndrome (poikiloderma congenitale) (Figure 27.32)	AR gene (rare)	- Facial poikiloderma (onset during the first year of life) - Acral keratoses, SCCs <i>Clue:</i> Strikingly erythematous cheeks that develop telangiectasia in infancy	- CE (short stature, hypogonadism, and cataracts) - Imaging studies (dental/skeletal defects and osteosarcomas) <i>DDs</i> - Bloom syndrome - Navajo syndrome
Werner syndrome	AR gene mutation	- Onset in second decade of life - Progeria adulatorum (premature aging) - Localized or diffuse hyperpigmentation with poikiloderma	- CE (gray hair and cataracts) - Laboratory and imaging studies (diabetes mellitus and atherosclerosis) <i>DDs</i> - Progeria (Hutchinson–Gilford pregeria syndrome)
Xeroderma pigmentosum	AR gene mutation	- Onset in early childhood - Malignancies (BCCs, SCCs, and melanoma) <i>Clue:</i> Severe photosensitivity with striking photoaging in a child	- CE (eye inflammation) - Imaging studies (central nervous system [CNS] cancer) <i>DD:</i> Cockayne syndrome
Acrodermatitis chronica atrophicans	Acquired ^{58,59}	- Months or years after tick assault - On extensor surfaces of lower extremities (occasionally on the trunk and rarely on the face)	- History of tick bite - LS (serology and PCR for <i>Borrelia</i>; culture from atrophic skin possibly positive for <i>Borrelia</i>) - Histology (plasmacytoid infiltrate and spirochetes detected with Warthin–Starry stain)
Cutaneous amyloidosis		Poikiloderma with deposits of amyloid in the skin - Late onset: During the fifth decade of life - Early onset: In association with lichenoid papules, photosensitivity, palmoplantar keratoses, and short stature (“poikiloderma-like cutaneous amyloidosis syndrome”)	Histology (poikilodermatous changes with deposition of amyloid; Congo red stain positive, apple-green birefringence)
Atopic dermatitis		- In adults predominantly on the lateral aspects of the neck - Chronic inflammation and application of topical corticosteroids are the main culprits	- History of chronic atopic dermatitis - Histology (spongiotic dermatitis and poikiloderma)
Dermatomyositis		Poikilodermatous picture on sun-exposed areas	Clinical and laboratory evidence of dermatomyositis <i>DD:</i> From other acquired poikilodermatous conditions, especially subacute cutaneous lupus erythematosus (SCLE)
Erythema ab igne		See acquired diffuse hyperpigmentation (Table 27.8) Poikiloderma is considered the end stage of cumulative skin alterations caused by prolonged exposure to heat	- CE - Histology (connective tissue degeneration, poikiloderma, and epithelial cell atypia)
Graft versus host disease (GVHD)		In chronic GVHD, extensive poikilodermatous involvement of the skin, along with severe mucosal reaction and sclerodermoid or lichenoid skin lesions	Almost never misdiagnosed because of history of bone marrow transplantation (less frequent in cases of other types of transplantation)

(Continued)

Table 27.11 (Continued) Poikilodermas.

Disorders	Acquired/inherited	Features and clues	Assessments/DDs
Hydroxyurea		- On sun-exposed areas predominantly - In patients with myeloproliferative disorders	History of treatment with hydroxyurea <i>DD:</i> Dermatomyositis
Lichen planus		One case: Generalized lichen planus–induced poikiloderma after chronic inflammation	- CE - Histology (poikilodermatous changes and lichen planus features)
Lupus erythematosus (LE)		Systemic LE: Resolution of acute erythematous lesions produces poikiloderma on sun-exposed areas	- History of acute lupus - Histology - Serologic tests
		<i>SCLE</i> ⁶⁰ - A few cases reported - One case after sunburn - Large plaques on chest, back, and extensor aspects of arms (sun-exposed areas)	- Typical SCLE lesions - Histology - Serologic tests <i>DD:</i> From other acquired poikilodermatous conditions, especially dermatomyositis
		<i>Discoid LE</i> Telangiectoid variant of DLE	- Histology - Serologic tests
		<i>Neonatal LE</i> Resolution of lesions results in poikiloderma	- Histology - Serologic tests (mother and baby)
		<i>Lupus panniculitis</i> Resolution of lesions results in poikiloderma	- Histology - Serologic tests
Mycosis fungoides (MF) (Figure 27.33)		<i>Poikilodermatous variant</i> ⁶¹ Coexistence of poikiloderma and patches/plaques of classic MF <i>Clue:</i> Breasts and hips typically affected	<i>Poikilodermatous variant</i> - Histology (typical MF changes and poikiloderma) - Immunophenotype: CD4+ pattern (CD2+, CD3+, CD4+, CD45RO+ CD8–, and CD7–) and rarely CD8+ pattern
		<i>Granulomatous MF with poikiloderma</i> One case reported; poikiloderma, erythematous plaques, and ichthyosis	<i>Granulomatous MF with poikiloderma</i> Histology (granulomatous reaction with giant cells and epidermotropism of atypical lymphocytes)
Parapsoriasis (large plaque)		Lower aspect of trunk, upper thighs, and major flexures typically affected	Histology (mild dermatitis, dermal band-like lymphocytic infiltrate, and atrophic epidermis) <i>DD:</i> MF
Poikiloderma atrophicans vasculare (poikilodermatous variant of cutaneous T-cell lymphoma)		- Considered poikilodermatous variant of MF with indolent course - Poikiloderma on trunk and flexures - Onset in early adulthood - Male predominance <i>Clues</i> - Absent or mild pruritus - Stinging sensation rather than pruritus	- Histology (MF-like histology plus poikilodermatous features) - Immunophenotype (CD8+/CD4– predominantly) <i>DDs</i> - MF - Large plaque parapsoriasis - Connective tissue diseases - Corticosteroid-induced poikiloderma
Topical corticosteroid use		<i>Clue:</i> Localization in previously affected and treated area	History of prolonged application of corticosteroids
Photoaged skin (dermatoheliosis)		- Poikiloderma on sun-exposed areas - Distribution depending on type of exposure (occupational or habitual) - High risk for skin cancer <i>Clue:</i> Wrinkling, skin laxity, large comedones	- CE - History of chronic sun exposure - Histology (solar elastosis)
Poikiloderma of Civatte		See Table 27.12	
Radiodermatitis		- Late reaction restricted to site of irradiation - Appears months or even years later - Poikiloderma is a sign of extensive skin damage	Not easy to misdiagnose because of medical history

Abbreviations: AD = Autosomal dominant; AR = autosomal recessive; CE = clinical examination; DD = differential diagnosis; LS = laboratory studies.

Table 27.12 Facial hyperpigmentation.

Lesions/disorders	Features and clues	Assessments/DDs
Melasma ⁶²	See Chapter 5	• CE (typical distribution) • Evaluation of melasma depth with Wood's lamp examination currently debatable <i>DD:</i> Every facial macular hyperpigmented lesion
Riehl's melanosis ⁶³	• Pigmented photocontact dermatitis (restricted in sites of cosmetic application) • Brown-gray color (dermal melanin) <i>Clue</i> • Primary phase of irritation	• CE • History <i>DDs</i> • Melasma • Postinflammatory hyperpigmentation
Nevus of Ota (see Table 27.6) (circumscribed hyperpigmentation)		
Nevus of Hori (see Table 27.6) (circumscribed hyperpigmentation)		
Periorbital hyperpigmentation	<i>Familial periorbital hyperpigmentation</i> • Onset during puberty • Inheritance speculated <i>Clue:</i> Lower eyelid initially affected	<i>Familial periorbital hyperpigmentation</i> • Familial history • Dark skin color <i>DD:</i> Other causes of "dark circles," especially atopic dermatitis
	<i>Periorbital hyperpigmentation in atopics</i> <i>Clue:</i> Dark purplish-gray hyperpigmentation (atopic shiners)	<i>Periorbital hyperpigmentation in atopics</i> • Color contrast of periorbital circles in pale face <i>DDs</i> • Familial periorbital hyperpigmentation • Postinflammatory hyperpigmentation • Systemic disorders (e.g., anemia and endocrine disorders) • Acanthosis nigricans
Pigmented peribuccal pigmentation	• Predilection for middle-aged women • Etiology: Postinflammatory pigmentation of perioral dermatitis, photodynamic reaction caused by cosmetics <i>Clue:</i> Narrow perioral rim spared	• Fading after discontinuation of culprit agent
Exogenous ochronosis ^{64,65}	• Adverse effect of chronic use of hydroquinone cream on the face (occasionally hands) • Usually in black women <i>Clue:</i> Caviar-like papules (pigmented colloid milium)	• History of chronic and excessive application of hydroquinone-containing creams in various concentrations • Histology (brownish-yellow "banana-shaped" fibers in papillary dermis) <i>DDs in black individuals</i> • Dermatitis papulosa nigra • Pigmented colloid Milium caused by other chemicals (phenol, picric acid, resorcinol, fertilizers, and mercury)⁶⁶
Dermatitis papulosa nigra	• Familial predisposition • Small brown-black papules on cheeks and forehead (also seen on neck, chest, and back) <i>Clue:</i> Africans and dark-skinned racial groups affected	• CE • Histology <i>DDs</i> • Seborrheic keratoses • Acrochordons • Adnexal tumors • Nevi • Exogenous ochronosis • Verrucae

(Continued)

Table 27.12 (Continued) Facial hyperpigmentation.

Lesions/disorders		Features and clues	Assessments/DDs
Lichen planus pigmentosus		See Chapter 7 - Gray-brown macules on sun-exposed and intertriginous areas - Middle-aged individuals - Phototypes III and IV <i>Clue:</i> No preceding erythematous phase	- CE (typical distribution) - Histology <i>DD:</i> Erythema dyschromicum perstans
Actinic lichen planus		- More frequently seen in young individuals (Middle East) on sun-exposed areas - During spring and summer - Red-brown plaques on the face, neck, and dorsal aspects of hands or melasma-like lesions	- History - CE - Histology <i>DD:</i> Melasma
Poikiloderma of Civatte ⁶⁷ (Figure 27.34)		- Typical triad of poikiloderma present - Distribution indicative of photodamage; lateral aspects of neck, decollete area, and peripheral face - Extrafacial–extracervical case report: Contact sensitization to fragrances⁶⁸ - Predominantly in women <i>Clue:</i> Submandibular and submental (anatomically shaded) areas spared	CE <i>DD:</i> Erythromelanosis follicularis of face and neck
Erythromelanosis follicularis of face and neck		- Reddish-brown pigmentation and telangiectasia in typical distribution (in front of and beneath the ear and lateral aspects of the neck) - Familial occurrence - Predominantly in men <i>Clue:</i> Pale follicular papules (nonkeratotic)	CE <i>DD:</i> Poikiloderma of Civatte
Fixed drug eruption		See Table 27.6	
Postinflammatory hyperpigmentation (PIH)		See Chapter 15	
Oncology	Solar lentigo	See above	Dermoscopy
	Pigmented actinic keratosis ^{69,70}	Pigmented variant of actinic keratosis	Dermoscopy (<i>inner gray halo</i> surrounding the follicular openings) <i>DD:</i> Lentigo maligna
	Seborrheic keratosis	See above	CE and dermoscopy
	Lentigo maligna	Melanoma	Dermoscopy (asymmetric, pigmented follicular openings), and if doubt remains, perform biopsy

Abbreviations: CE = clinical examination; DD = differential diagnosis.

Patients with facial hyperpigmentation are an every-day routine for the dermatologist. Differentiating the facial lesion is crucial, as usual (Table 27.12), because this spectrum and malignancy intersect in the case of lentigo maligna. The photoaged face almost always presents with more than one hyperpigmented lesions. These form a field of clinically hardly distinguishable conditions with a subsequent diagnostic challenge for the physician. Dermoscopy may provide the solution in such cases. The face is always examined together with the neck, so usually both face and neck pigmentation are described with the term *facial*.

In cases of hyperpigmentation resembling characteristic patterns of Addison disease and pellagra (Table 27.13), systemic disorders should be suspected. Extracutaneous signs and symptoms like malaise, weight loss, arthralgias, abdominal pain, headaches, and palpitations are evaluated as possible components of a systemic condition. The detailed physical examination and a variety of laboratory and imaging studies facilitate the diagnosis. Patients who provide information about a current or a preceding discontinued treatment should be assessed as possible cases of drug-induced hyperpigmentation, a diagnosis that is



Figure 27.4 Neurofibromatosis type 1. (Courtesy of E. Rallis.)



Figure 27.5 Facial angiofibromas in a patient with tuberous sclerosis. (Courtesy of E. Rallis.)



Figure 27.6 Mongolian spot. (Courtesy of E. Rallis.)



Figure 27.7 Giant congenital melanocytic nevi. (Courtesy of E. Rallis.)

definitely easier than chemical-induced hyperpigmentation (Table 27.14). Exposure to a chemical agent might have been insidious with a latent time of months, even years. Chemical ingestion or exposure is environmental, nutritional, occupational, or iatrogenic.

Hyperchromia and hyperpigmentation exhibit mainly brown and black, but also gray and blue colors. As mentioned above, the blue color corresponds predominantly to subepidermal melanocytes. When a brown or black chromophore is embedded underneath the epidermis, then blue color is expected as well. This also applies to subcutaneous nodules that do not contain dark chromophores. The correct diagnosis of blue conditions (Table 27.15) is crucial. A diagnostic challenge, but also a pitfall, may be hidden in either a circumscribed or a diffuse discoloration; “malignant blue color” corresponds to melanomas and diffuse melanosis cutis, a rare presentation of metastatic melanoma.

Table 27.13 Hyperpigmentation in systemic disorders (endocrine, nutritional, metabolic, and autoimmune disorders and toxicity).

Disorders/conditions		Features and clues	Assessments/differential diagnoses
Pellagra-like pattern of distribution	Pellagra	• Photosensitivity results in violaceous plaques on vface, neck (Casál necklace), and back of hands and feet • Produced by reduced nutritional uptake of niacin (malnutrition, alcoholism, and malabsorption)	• Laboratory tests (N'-methyl-niacinamide and pyridine decreased in urine) <i>DDs</i> • Porphyria cutanea tarda • Phototoxic reactions • Kwashiorkor (in children) • Other pellagra-like hyperpigmentations (listed here)
	Carcinoid syndrome	• Caused by functioning paracrine tumor • Etiology of hyperpigmentation: Tryptophan forms 5-hydroxytryptamine and not niacin	• Laboratory tests (5-HIAA in urine) • Imaging studies (e.g., OctreoScan)
	Hartnup disease	• AR disorder • Abnormality in renal tryptophan transport	
	Isoniazid (INH) treatment	INH-induced NAD production by niacin	• History
Addison-like pattern	Addison disease	• Increase in ACTH levels due to adrenal cortex insufficiency (ACTH–cortisol negative feedback absent) • Diffuse hyperpigmentation • More intense on sun-exposed and flexural areas • Mucosal surfaces frequently involved <i>Clue:</i> Hyperpigmented creases of palms and soles	• CE (fatigue and weight loss) • Laboratory confirmation (plasma cortisol level and ACTH stimulation test) <i>DDs</i> From other Addison-like hyperpigmented disorders (listed here)
	ACTH administration ⁷¹	Iatrogenic	• Medical history
	Busulfan treatment	Iatrogenic (see Table 27.14)	• Medical history
	Pheochromocytoma	Adrenal or extra-adrenal tumors	• CE and history (hypertension, palpitations, headaches, and paroxysmal swelling of the neck)
	Cushing disease	• Noniatrogenic; result of ACTH-secreting tumor (e.g., adrenal tumors and ectopic production of ACTH by tumors) <i>Clue:</i> Iatrogenic Cushing syndrome not associated with pigmentary disorders	• Laboratory confirmation (plasma cortisol levels and ACTH stimulation test)
	Nelson syndrome	• Iatrogenic: After bilateral adrenalectomy • Hormonal replacement therapy not effective <i>Clues</i> Very dark hair, lentigines, and longitudinal melanonychia	• History
Other	Pregnancy/menstruation	Pregnancy • Melasma-type hyperpigmentation of face and neck • Darkening of anogenital skin and nipples • Linea alba converted to linea nigra <i>Clue:</i> Menstruation occasionally produces recurrent similar condition	• History
	Oral contraceptives	Melasma-type hyperpigmentation	• History
	Anemia	• B12 deficiency; mottled brown pigmentation of face, hands, and feet, especially in dark-skinned individuals (fingertips and nails occasionally affected) • Folic acid deficiency; diffuse brown hyperpigmentation	• Laboratory confirmation and investigation of anemia

(Continued)

Table 27.13 (Continued) Hyperpigmentation in systemic disorders (endocrine, nutritional, metabolic, and autoimmune disorders and toxicity).

Disorders/conditions		Features and clues	Assessments/differential diagnoses
	Vagabond disease	- Older individuals - Hyperpigmentation at intertriginous sites and hypopigmented macules <i>Clue:</i> Signs of malnutrition, lack of cleanliness, and chronic pediculosis	CE Pediculosis corporis
	Whipple disease	- Up to 50% of patients exhibit diffuse hyperpigmentation - Pathogen is <i>Tropheryma whipplei</i>	- CE (arthralgias, abdominal pain, steatorrhea, and diarrhea) - LS
	Congenital adrenal hyperplasia	- Hyperpigmentation occurs in severe cases - Hyperpigmentation evident at birth or during infancy (progressive)	- Striking clinical evidence of the disorder (pseudohermaphrodite, growth retardation, early epiphyseal closure, and precocious puberty) - Laboratory confirmation and imaging studies
	Renal failure	- Diffuse and generalized - More prominent on face and hands - Reduced clearance of β-melanocyte-stimulating hormone (β-MSH); deposition of additional chromophores, e.g., carotenoids	Laboratory confirmation (abnormal renal function)
	Hemochromatosis	- Primary (AR gene; clinical picture accelerated by excessive alcohol intake) - Secondary (blood transfusions, excessive ingestion of iron) - Diffuse bronze-gray discoloration	- Relevant history - Laboratory confirmation (serum ferritin and serum iron) - Assessment of possible liver disease and diabetes <i>DDs</i> - Addison disease - Argyria
	Cirrhosis (especially primary biliary cirrhosis)	Diffuse, especially on sun-exposed areas	- History - LS (disorganization of liver function and architecture)
	Wilson disease	- AR disorder characterized by copper deposition - Gray-brown hyperpigmentation <i>Clues</i> - Blue lunulae - Kayser–Fleischer ring (yellow-brown ring in cornea)	- Laboratory confirmation (serum ceruloplasmin and urinary copper) - Liver biopsy <i>DDs</i> - Hepatic disease - Gaucher disease
	Kwashiorkor	- Protein deficiency caused by malnutrition (children typically affected) or malabsorption - Hyperpigmentation admixed with hypopigmentation - Preceding inflammatory lesions observed <i>Clues</i> - Flag sign in hair - Rotund abdomen; edema because of hypoalbuminemia	Clinical and laboratory findings (hypoalbuminemia)

Abbreviations: AR = autosomal recessive; CE = clinical examination; DDs = differential diagnoses; LS = laboratory studies.

Table 27.14 Drug- and chemical-induced hyperpigmentation (synopsis).

Lesions/disorders	Localization and distribution			Color	Other features and chromophores
	Skin	Mucosa	Nails/hair		
Amiodarone ⁷²	Sun-exposed areas (especially face)			Purplish to gray	- Typically in fair-skinned individuals (phototype I) after long-term treatment; tendency to fade after discontinuation of the agent - Lipofuscin in macrophages, mast cells, keratinocytes, endothelial cells, fibroblasts, amiodarone–phospholipids, and insoluble compounds
Antimalarials (chloroquine, hydroxychloroquine, and quinacrine)	Pretibial areas, face	Oral mucosa (hard palate), sclerae	Subungual area	Blue-black or gray (yellow-brown in case of quinacrine)	- Tendency to fade (<i>but not resolve</i>) - Drug–melanin compounds/perivascular hemosiderin
Antimetabolites ^{73,74}	<i>5-FU</i> Sun-exposed areas, serpentine supragenous hyperpigmentation (over veins of administration), diffuse reticulate hyperpigmentation, serpentine streaks in the back, buttocks, and palms/soles		<i>5FU</i> Melanonychia (diffuse, transverse, half and half–like nails)	Brown	<i>5-FU</i> - Tendency to fade over time; occasional recurrence after reexposure - Melanin
	<i>Capecitabine</i> ^{75,76} Acral hyperpigmentation (diffuse, along creases or macular)	<i>Capecitabine</i> Oral mucosa (tongue and gingiva)	<i>Capecitabine</i> Longitudinal melanonychia		<i>Capecitabine</i> - Predilection for phototypes IV and V; resolution months after cessation of therapy; parallel ridge pattern in acral lesions sparing eccrine gland apertures - Melanin (epidermis)
	<i>Tegafur</i> ^{77,78} Acral hyperpigmentation (diffuse, along creases or macular), face (macular)	<i>Tegafur</i> Oral mucosa (tongue and lips), glans penis	<i>Tegafur</i> Longitudinal melanonychia		<i>Tegafur</i> - Tendency to fade after cessation of treatment - Melanin (epidermis)
	<i>Methotrexate</i> Photodistributed hyperpigmentation		<i>Methotrexate</i> Hair pigmentation (“flag sign” in blond hair corresponds to weekly therapy)		<i>Methotrexate</i> Melanin
Antitumor antibiotics ^{73,74}	<i>Bleomycin</i> Flagellate pattern (after scratching), patches in sites of pressure and linear pigmentation in palmar creases		<i>Bleomycin</i> Transverse melanonychia	Brown	<i>Bleomycin</i> - Resolution after treatment cessation - Melanin (epidermis, dermal melanophages)

(Continued)

Table 27.14 (Continued) Drug- and chemical-induced hyperpigmentation (synopsis).

Lesions/disorders	Localization and distribution			Color	Other features and chromophores
	Skin	Mucosa	Nails/hair		
Antitumor antibiotics ^{73,74}	<i>Dactinomycin</i> (<i>actinomycin D</i>) ⁷⁹ Diffuse (especially on face), macules–patches in flexures			Brown	<i>Dactinomycin</i> • Tendency to fade after cessation of treatment • Melanin (nonspecific postinflammatory hyperpigmentation)
	<i>Daunorubicin</i> ⁸⁰ Diffuse on sun-exposed areas or generalized, melanotic macules on trunk and extremities, polycyclic pigmentation of scalp		<i>Daunorubicin</i> Melanonychia (transverse)		<i>Daunorubicin</i> • Tendency to fade after drug cessation; recurrence after retreatment possible • Melanin (epidermis)
	<i>Doxorubicin</i> ⁸¹ Palms and soles, over interphalangeal joints of fingers, macules on trunk and extremities	<i>Doxorubicin</i> Oral mucosa (tongue and buccal mucosa)	<i>Doxorubicin</i> Melanonychia		<i>Doxorubicin</i> • Tendency to fade after drug cessation • Melanin (epidermis and melanophages)
Alkylating agents ^{73,74}	• <i>Cyclophosphamide</i> Patches on acral skin	<i>Cyclophosphamide</i> Gingiva (and teeth), tongue (one case reported; in combination with doxorubicin)	<i>Cyclophosphamide</i> Melanonychia, darkening of light-colored hair	Brown	<i>Cyclophosphamide</i> • Appearance after 4 weeks of treatment • Tendency to fade 6–12 months after discontinuation
	• <i>Ifosfamide</i> Hands/feet, flexures, scrotum, under occlusive dressings; diffuse with large lesions on trunk				<i>Ifosfamide</i> • Appearance after one course or several months of treatment; fading despite treatment possible; persisting despite drug cessation also possible
	• <i>Thiotepa</i> Circumscribed and restricted to areas covered by occlusive dressings				<i>Thiotepa</i> Gradual fading possible
	<i>Mechlorethamine</i> (<i>nitrogen mustard</i>) Circumscribed to areas of topical application				<i>Mechlorethamine</i> • Melanin
	<i>BCNU</i> (<i>carmustine</i>) Circumscribed at sites of topical treatment with BCNU				<i>BCNU</i> • Melanin
	<i>Busulfan</i> Diffuse on face, forearms, chest, and abdomen or generalized/ accentuated on trunk, face, and hands				• Dark-skinned individuals more frequently affected' regression after treatment cessation and recurrence after reexposure possible; Addison-like pattern of hyperpigmentation • Melanin (epidermis)
Diltiazem	Sun-exposed areas (intense color on perifollicular skin)			Slate-gray to gray-brown	• Predilection for dark-skinned individuals • Melanin (melanophages)
Eltrombopag ⁸²	Diffuse hyperpigmentation on face, arms, and legs			Gray	• Persistent hyperpigmentation during treatment

(Continued)

Table 27.14 (Continued) Drug- and chemical-induced hyperpigmentation (synopsis).

Lesions/disorders	Localization and distribution			Color	Other features and chromophores
	Skin	Mucosa	Nails/hair		
Heavy metals	<i>Arsenic (As, metalloid)</i> Diffuse (pattern of “raindrops on a dusty road”), most prominent on trunk			<i>Arsenic</i> Brown-bronze (mottled)	<i>Arsenic</i> • Palmoplantar keratoses, BCC, Bowen disease, internal malignancies • Melanin (epidermis); arsenic (epidermis, dermis)
	<i>Bismuth (Bi, transition metal)</i> Diffuse/generalized	<i>Bismuth</i> Gingival margin (linear discoloration), oral mucosa, conjunctiva		<i>Bismuth</i> Blue-gray	• Bismuth granules detected throughout the dermis
	<i>Gold (Au, transition metal)</i> Sun-exposed areas (chrysiasis), periorbital skin			<i>Gold</i> Blue to slate-gray	• Gold granules in melanophages around vessels and eccrine glands (gold particles larger than silver particles)
	<i>Iron (Fe, transition metal)</i> In sites of topical application (Monsel's solution) or infusion			<i>Iron</i> Brown, red-brown	• Iron (among collagen fibers and in macrophages)
	<i>Lead (Pb, transition metal)</i> Diffuse	<i>Lead</i> Gingival margin (linear discoloration)	Nail discoloration	• Lead hue” (mixture of pallor and lividity) • Blue-black (gingiva)	• Lead granules (converted to lead sulfide)
	<i>Mercury (Hg, transition metal)</i> Diffuse, accentuated in skinfolds (after percutaneous absorption; rare nowadays)	<i>Mercury</i> Gingival margin (pigmented line similar to those observed in lead and bismuth toxicity)		• Slate-gray (skin) • Blue-black (gingiva)	• Mercury granules (free among collagen fibers and around vessels or in melanophages); melanin (epidermis)
	<i>Silver (Ag, transition metal)</i> Diffuse/generalized after ingestion (argyria; increased in sun-exposed areas, decreased in skinfolds), localized (after topical application of silver sulfadiazine)	<i>Silver</i> Mucosal surfaces (and sclerae)	<i>Silver</i> Nail discoloration (diffuse or limited to lunulae)	<i>Silver</i> Blue to slate-gray	<i>Silver</i> • Appearance months or years after ingestion • Silver (particles observed in sweat glands, basement membrane, hair follicles, and vessels; predilection for elastic fibers)
Hydroquinone	Areas of application (exogenous ochronosis)			Blue-black to black (caviar-like) papules	• Predilection for dark-skinned people, especially blacks; more frequent in Africa than in the United States (intense sunlight and additional chemical compounds thought to be possible culprits) • Yellow-brown “banana-shaped” bundles in dermis (degenerated collagen and accumulation of oxidation products of homogentisic acid)

(Continued)

Table 27.14 (Continued) Drug- and chemical-induced hyperpigmentation (synopsis).

Lesions/disorders	Localization and distribution			Color	Other features and chromophores
	Skin	Mucosa	Nails/hair		
Hydroxyurea ^{83,84}	Diffuse or in sites of pressure	Diffuse oral pigmentation (and perioral)	Melanonychia (diffuse, longitudinal, transverse, blue lunulae)	Brown	• Development usually after months of therapy; resolution after discontinuation • Melanin
Imatinib ^{85,86}	Diffuse or circumscribed (macules or patches)	Gingiva (and teeth), hard palate	Melanonychia, repigmentation of white hair (paradoxical hyperpigmentation)	Brown	• Persistent hyperpigmentation possible • Melanin (epidermis, melanin incontinence, and melanophages)
Minocycline ⁸⁷	Localized in scars, in sites of preceding inflammation, and on extensor surfaces of lower legs and forearms or diffuse on sun-exposed skin	Oral mucosa (and teeth), sclerae, lips	Nail discoloration	• Blue-black (in acne scars) • Blue-gray (in photoinduced pigmentation and in oral mucosa)	• Development after months of treatment; resolution after cessation of the therapy • Melanin, hemosiderin, minocycline (deposits of the drug or a metabolite)
Oral contraceptives	Melasma, nipples	Genital mucosa		Brown	• Melanin (hypermelanocytosis)
Phenothiazines (especially chlorpromazine)	Sun-exposed skin		Discoloration of nail bed	Blue-gray or purple-gray metallic color	• Deposits on sclera and cornea (hazy brown discoloration) and central lens opacities (brown) • Chlorpromazine–melanin complexes
Platinum agents (cisplatin) ⁸⁸	Circumscribed and patchy hyperpigmentation, especially in sites of pressure and minor trauma	Oral mucosa (patches)	Hair color change/ melanonychia	Brown	• Development early in therapy; usually permanent
Psoralens (psoralen–ultraviolet A [PUVA] or phytophotodermatitis)	Diffuse or circumscribed after topical exposure to psoralen-containing agents or plants			Brown	• Melanin
Tricyclic antidepressants (imipramine and desipramine) ⁸⁹	Diffuse (on sun-exposed skin)			Slate-gray, purple, dark brown	• Sulfur-containing golden brown bodies in dermis (pheomelanin–drug metabolite complex)
Zidovudine ⁹⁰	Diffuse or generalized, accentuated on flexures, knuckles (friction and pressure), and face (sun exposure)	Oral macules (tongue)	Melanonychia (more frequently longitudinal), blue lunulae	Brown	• Observed in darkly pigmented individuals; tendency to fade after drug cessation • Melanin (epidermis, melanophages)

Note: General information was extracted from Refs. 91 and 92.

Table 27.15 Blue color: Lesions and disorders.

Blue nevus Nevus of Ota Nevus of Ito Nevus of Hori Mongolian spot Foreign bodies and tattoos Maculae ceruleae (pediculosis pubis) Cyst Hidrocystoma Subcutaneous nodule Melanoma Venus lake and vascular neoplasms	Circumscribed
Ochronosis (alkaptonuria and exogenous) Drug-induced blue color (e.g., chlorpromazine and minocycline) ⁹¹	Diffuse or circumscribed
Heavy metal-induced blue color (argyria and chrysiasis) Lysosomal storage diseases Cyanosis and methemoglobinemia Diffuse melanosis cutis	Diffuse



(a)



(b)

Figure 27.9 (a) Becker nevus on the right shoulder. (Courtesy of M. Kyriazopoulou.) (b) Becker nevus on the chest. (Courtesy of E. Rallis.)



Figure 27.8 Labial melanocytic macule. (Courtesy of M. Kyriazopoulou.)

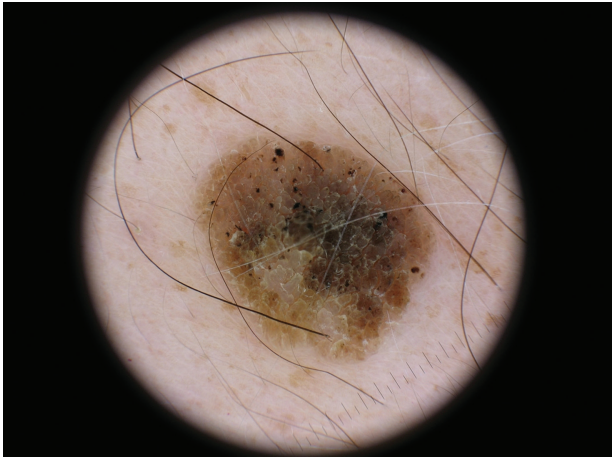


Figure 27.10 Dermoscopy of SK. (Courtesy of E. Rallis.)



Figure 27.11 Dermatofibroma. (Courtesy of E. Rallis.)



(a)



(b)

Figure 27.12 (a) Acral melanoma. (Courtesy of E. Rallis.)
(b) Dermoscopy of acral melanoma. (Courtesy of E. Rallis.)

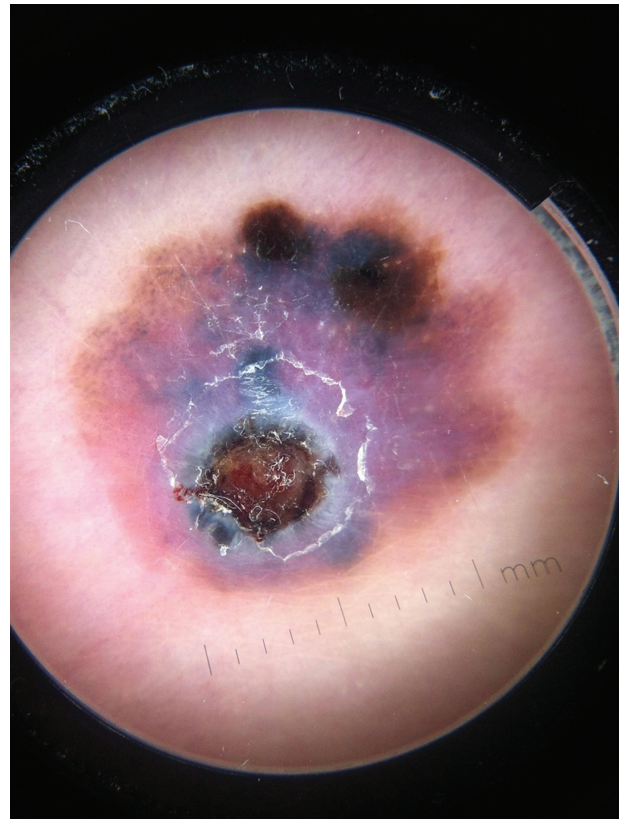


Figure 27.13 Dermoscopy of melanoma. (Courtesy of M. Kyriazopoulou.)



Figure 27.14 Postinflammatory hyperpigmentation. (Courtesy of E. Rallis.)



Figure 27.15 Multifocal fixed drug eruption owing to nimesulide. (Courtesy of E. Rallis.)



Figure 27.18 Epidermal nevus. (Courtesy of E. Rallis.)



Figure 27.16 Lichen planus pigmentosus. (Courtesy of E. Rallis.)



Figure 27.19 Incontinentia pigmenti. (Courtesy of E. Rallis.)

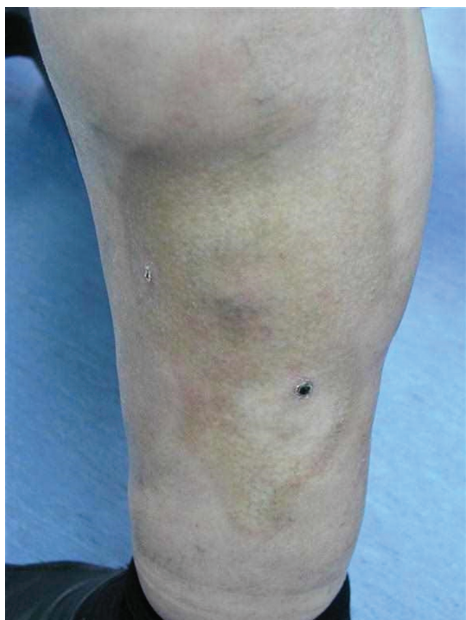


Figure 27.17 Atrophoderma of Pasini-Pierini. (Courtesy of E. Rallis.)



Figure 27.20 Acanthosis nigricans. (Courtesy of E. Rallis.)



Figure 27.21 Gougerot-Carteaud syndrome. (Courtesy of E. Rallis.)



Figure 27.24 Erythema ab igne. (Courtesy of E. Rallis.)



Figure 27.22 Phytodermatitis from fig tree. (Courtesy of E. Rallis.)



Figure 27.25 Flagellate dermatitis owing to bleomycin. (Courtesy of M. Kyriazopoulou.)

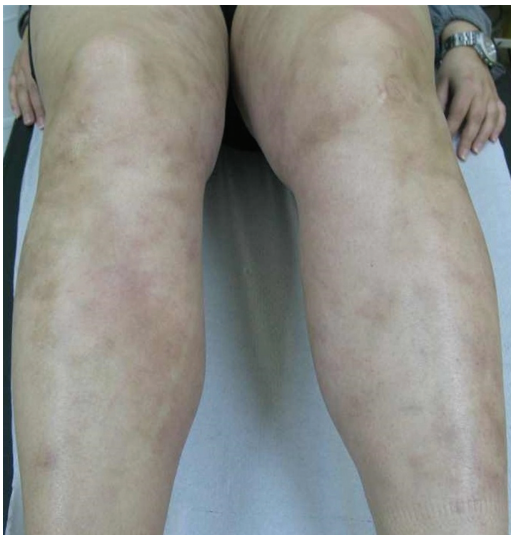


Figure 27.23 Methotrexate-induced hyperpigmentation. (Courtesy of E. Rallis.)



Figure 27.26 Pigmented purpura. (Courtesy of E. Rallis.)

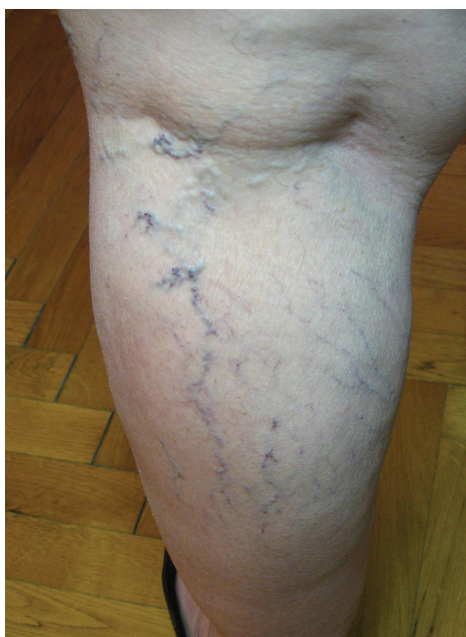


Figure 27.27 Chronic venous insufficiency. (Courtesy of E. Rallis.)



Figure 27.28 Urticaria pigmentosa—Darier sign. (Courtesy of E. Rallis.)



(a)



(b)

Figure 27.29 (a and b) Alkaptonuria—ashy ears. (Courtesy of E. Rallis.)

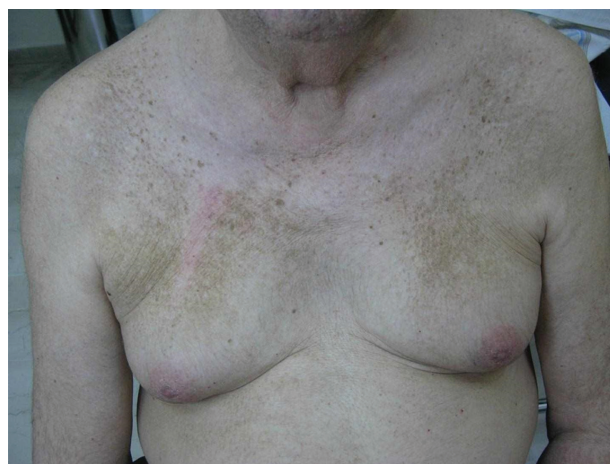


Figure 27.30 Terra firma-forme dermatosis. (Courtesy of E. Rallis.)



Figure 27.31 Tinea versicolor. (Courtesy of E. Rallis.)



Figure 27.33 Mycosis fungoides. (Courtesy of E. Rallis.)



Figure 27.32 Rothmund–Thomson syndrome. (Courtesy of E. Rallis.)



Figure 27.34 Poikiloderma of Civatte. (Courtesy of E. Rallis.)

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SECTION IV

Treatment

Cosmetic camouflage for pigmentation issues

28

ZOE DIANA DRAELOS

INTRODUCTION

The visual perception of even skin color leading to an attractive appearance is an interesting optical phenomenon. Light reflection from the skin surface and within the skin accounts for the blending of brown melanin, red hemoglobin, and yellow collagen. Subtle differences in melanin allow skin to appear almost black when the concentration is high and a reddish-white hue when the concentration is low. Melanin is produced in two forms: pheomelanin, a polymer of benzothiazine, which is red, and eumelanin, a polymer of dihydroxyindole, dihydroxyindole carboxylic acid, and their reduced forms, which is dark brown. Eumelanin is the ancestral brown-black melanin formed as an oblong or spherical granule about 0.9 microns long and 0.3 microns wide. Pheomelanin is the red-yellow pigment formed as a spherical granule about 0.7 microns in diameter. It is the various combinations of these two pigments that produce the diversity of beautiful skin colors that are subject to dyspigmentation. The challenge for the cosmetic chemist is to create the illusion of even appropriately pigmented skin in light of pigmentary abnormalities.

SKIN COLOR ISSUES

The primary cause of skin dyspigmentation is melanin production in response to sun exposure resulting in the tanning response.¹ This brownish pigmentation is temporary, but may in time lead to irregular skin melanization, a process better known as freckling. Increased melanin production can also occur in response to injury and hormone production, creating interesting hyperpigmentation patterns on the body and face. This induced melanogenesis may be epidermal or dermal, creating different abnormal skin hues.²

Epidermal melanogenesis, which is tan to brown in color, is attributed to the release and subsequent oxidation of arachidonic acid to prostaglandins, leukotrienes, and other inflammatory mediators, which initiate pigment production. If the inflammation disrupts the basal cell layer, the melanin is released and trapped by macrophages in the dermis. Dermal pigment, also known as pigmentary incontinence, is bluish-brown in Fitzpatrick skin types I–III and bluish-black in Fitzpatrick skin types IV–VI. These hues can create challenges for effective cosmetic camouflage.^{3,4}

COSMETICS AND CAMOUFLAGING

The most valuable cosmetic for camouflaging is facial foundation. Facial foundation is a pigmented moisturizer

that can be selected to match the skin color exactly, darken the depigmented or hypopigmented skin to the natural color, or lighten the hyperpigmented skin to match the natural surrounding skin. These facial foundations are available commercially at all mass merchandisers and cosmetic counters. In addition, specialty facial foundations are available specifically for camouflaging that are opaque, obscuring the underlying skin. The cosmetic selected depends on the severity of the pigmentation abnormality and whether depigmentation, hypopigmentation, or hyperpigmentation exists. This section examines the variety of facial foundations that can be employed for camouflage purposes.

FACIAL FOUNDATION FORMULATIONS

Facial foundations for camouflaging must possess a variety of qualities. They must cover the underlying skin to a greater or lesser degree, a quality known as coverage. In addition, the cosmetic must be long wearing and remain in place, a quality known as substantivity. Finally, the cosmetic should be water resistant, staying in place with sweating, tearing, exogenous water contact, and high-humidity conditions. There are four basic facial foundation formulations: oil-based, water-based, oil-free, and water-free forms. Each of these formulations will be discussed in the context of pigmentation abnormality camouflage.

Oil-based foundations

Oil-based foundations are water-in-oil emulsions, meaning that the ingredient in largest concentration is oil into which the water has been emulsified, usually with a low-concentration surfactant. Since oil is in highest concentration, these foundations are more water resistant and are better suited for camouflaging purposes since they do not slide off the face with perspiration. In addition, higher pigment concentrations can be added into the formulation to better obscure the underlying skin. These products usually contain mineral oil and water. The liquid is spread over the skin, followed by evaporation of the water, leaving behind a thin pigment and oil film. While the water is evaporating, the film can be moved around with a sponge or the fingers to blend into the surrounding skin, which is important when camouflaging localized pigmentation defects. Oil-based foundations also leave the skin with a moist feeling, especially desirable in dry complected patients.

Oil-based foundations can be used to camouflage all types of mild to moderate pigmentation defects with ease and high patient satisfaction. For patients with

hypopigmentation, a slightly darker to exact match facial foundation can be used over the lighter skin area and then blended into the surrounding skin depending on the degree of pigment loss. For hyperpigmentation, a slightly lighter to exact match facial foundation can be selected. If facial foundation is to be applied over the entire face, an exact match is preferred as less blending is required.

Oil-based facial foundations can be formulated as liquids and creams, depending on the viscosity of the formulation. Creams contain more pigment than liquids and provide better camouflaging, but are thicker and more occlusive on the skin surface, imparting a more theatrical appearance. Professional camouflaging cosmetics, discussed later in this chapter, are of this type.

Water-based foundations

Water-based facial foundations are oil-in-water emulsions containing a small amount of oil in which the pigment is emulsified with a relatively large quantity of water. The primary emulsifier is usually triethanolamine or a nonionic surfactant. The secondary emulsifier, present in smaller quantity, is usually glyceryl stearate or propylene glycol stearate. This is the most popular facial foundation formulation as the water evaporates quickly, leaving behind a thin pigment film over the face. These foundations are good for patients with oily skin, but have little water resistance and are easily removed with perspiration and tearing. The pigment concentration is lower; thus, their ability to camouflage is restricted to very mild to mild dyspigmentation.

Oil-free foundations

Oil-free facial foundations contain no animal, vegetable, or mineral oils and are based on silicone derivatives, such as dimethicone. Dimethicone is an oil into which the pigment is dissolved. Water is in highest concentration, making this formulation a variant of the oil-in-water formulation previously discussed. Oil-free facial foundations are best for patients with oily or acne-prone skin who need camouflaging of very mild to mild dyspigmentation.

Anhydrous foundations

Anhydrous facial foundations contain no water, which is the meaning of the word anhydrous. Vegetable oil, mineral oil, lanolin alcohol, and synthetic esters form the oil phase, which may be mixed with waxes to form a cream.⁵ They can be dipped from a jar, squeezed from a tube, wiped from a compact, or stroked from a stick. These foundations dry down very slowly and have a long playtime. The playtime is the amount of time available to move the facial foundation over the face until it dries or sets into place. After this time, the film can no longer be moved or modified. Facial camouflaging may require blending of the facial foundation over and around the dyspigmentation. Anhydrous facial foundations offer waterproof camouflaging and can be worn successfully in humid conditions and when swimming. However, a special removal product

is necessary as soap and water will not completely remove the cosmetic.

FACIAL FOUNDATION PIGMENTS AND SPECIALTY ADDITIVES

Facial foundations contain a variety of pigments to camouflage the underlying skin. The coloring agents in all facial foundations are based on titanium dioxide with iron oxides, occasionally in combination with ultramarine blue. Titanium dioxide is a white pigment acting both as a pigment concealing agent and a physical sunscreen. Many camouflaging facial foundations offer excellent photoprotection, which can be helpful in shielding the skin from ultraviolet (UV) exposure, minimizing additional dyspigmentation.⁶ Iron oxide also provides some photoprotection, but it is a brown pigment and is added in the appropriate amount to match the skin color. More iron oxide creates a darker facial foundation suitable for higher Fitzpatrick skin types while less iron oxide creates a lighter facial foundation to match the lower Fitzpatrick skin types.

Facial foundations contain a variety of other additives designed to impart unique properties to the formulations. Facial foundations also contain talc, which is a powder added to the formulation to create an even particulate film over the skin surface. It is the talc left behind after the water evaporates in liquid facial foundations that creates the smooth feel and visual skin uniformity of the cosmetic. Kaolin may also be added to oil control facial foundations to absorb sebum and perspiration. Sebum and perspiration allow the talc particles to migrate over the face, destroying the even film and camouflaging abilities of the foundation. Other absorbing substances, such as starch or polymers, may be added to enhance the longevity of the facial foundation film on the face.⁷ Once the film is destroyed, the foundation can no longer effectively camouflage underlying dyspigmentation.

FACIAL FOUNDATION CAMOUFLAGING PROPERTIES

The ability of a foundation to conceal or cover the underlying skin is known as “coverage.” Optimal coverage is desirable when using facial foundation for camouflaging purposes. The amount of coverage required depends on the degree of skin dyspigmentation. Very dark or very light dyspigmented skin will require higher coverage facial foundations to camouflage. In general, it is more difficult to camouflage darker skin dyspigmentation than lighter skin dyspigmentation.

The coverage of a foundation is directly related to the amount of titanium dioxide, zinc oxide, talc, kaolin, and precipitated chalk it contains. Titanium dioxide is the best agent to achieve optimal coverage, but high concentrations of titanium dioxide will make the facial foundation thick and pasty. Zinc oxide is also a white pigment that can be added to titanium dioxide to improve the texture and the spreadability of the foundation. Spreadability is the ease with which the foundation can be rubbed into a thin film over the facial skin. Titanium dioxide and zinc

oxide are the same ingredients that are used as inorganic physical blocks. Kaolin and precipitated chalk are finer-particle white pigments that can be blended with titanium dioxide and zinc oxide to improve the smoothness of the facial foundation film as it glides over the skin. By varying the concentration of these white particulates, the cosmetic chemist can create various facial foundation aesthetic characteristics.

The coverage of a facial foundation can also determine the endogenous SPF of the formulation. This is important, as solar radiation is the cause of skin dyspigmentation, including lentigines, melasma, post-inflammatory hyperpigmentation following sunburn, and so on. In addition, many skin lightening preparations function by inhibiting key steps in melanin production, such as the rate-limiting enzyme tyrosinase. Since tyrosinase is stimulated by UV radiation, superior photoprotection may enhance the efficacy of prescription or over-the-counter (OTC) skin lightening preparations. Thus, the cosmetic used for camouflaging may also provide therapeutic benefits, as well, encouraging the patient to consider wearing facial cosmetics to speed up appearance improvement. In general, sheer coverage foundations with minimal titanium dioxide, which are almost transparent, possess an SPF of around 2. Moderate-coverage foundations are translucent and provide an SPF of 4 to 5. Finally, anhydrous high-coverage foundations, which are waterproof and contain large amounts of titanium dioxide, are opaque and function as a total physical sunblock. These anhydrous formulations provide the best coverage and the best sun protection simultaneously.

FACIAL FOUNDATION APPLICATION VARIETIES

Facial foundations are available in a variety of forms: liquid, mousse, water-based cream, anhydrous cream, stick, and cake.⁸ All of these varieties can be used for camouflaging, depending on the amount of titanium dioxide, zinc oxide, talc, and kaolin they contain. It is easier to put higher concentrations of these ingredients in higher-viscosity products; hence, in general, thin liquids do not camouflage as well as thick creams.

Of the facial foundations, liquid formulations are most popular because they are the easiest to apply. The liquid is poured from the bottle onto the fingertips, dabbed from the bottle on a brush, or dispensed onto a sponge. The liquid must be immediately rubbed over the face to create an even film before the water completely evaporates. For camouflaging, a facial foundation brush is recommended as the product can be easily dabbed and pushed with the tiny bristles around scars and into the pores. Liquid facial foundations provide sheer to moderate coverage and create a natural appearance, which is desirable. They are appropriate for mild dyspigmentation, but are not waterproof. If a liquid facial foundation is aerosolized, a foam foundation, known as a mousse, is produced.

Cream foundations are usually preferred for camouflaging purposes as they can create a thicker, more visually obstructive film over the area of facial dyspigmentation.

Cream foundations are available as water-based or water-free anhydrous formulations, which are waterproof.⁹ Professional camouflage cosmetics are anhydrous creams or sticks. They create a thick occlusive film over the skin surface containing abundant pigment to obscure visualization of the underlying skin.¹⁰ Unfortunately, the film is so thick that it obscures facial landmarks. This means that the use of other facial cosmetics, such as blush and lipstick, are required to complement the total facial adornment.

The thickest and most opaque of the facial foundations are the anhydrous cream wax-based sticks that are extruded into a rod and packaged in a roll-up tube. These are stick foundations. A second type of opaque foundation includes cream/powder foundations, consisting of talc, kaolin, precipitated chalk, zinc oxide, and titanium dioxide compressed into a cake that is applied to the skin with a dry sponge (powder) or moistened sponge (cream).¹¹ Most of the professional camouflaging cosmetics are of this type.¹²

CAMOUFLAGE COSMETIC APPLICATION

Camouflage cosmetics are designed to cover underlying pigmentation abnormalities, but they are not able to duplicate the appearance of a freshly washed, unadorned face. It is obvious to all that the individual is wearing a cosmetic. Therefore, camouflage cosmetics are designed to minimize facial defects while accentuating attractive features of the face, making them more suitable for women than men.¹³ Patients can learn the tricks to proper application of camouflaging cosmetics from paramedical camouflage artists, estheticians, dermatologists, and cosmetic consultants. The successful application of camouflage cosmetics requires a well-formulated, quality product applied with the skill of a stage makeup technician and the artistic abilities of a painter.

This chapter will focus on the application of camouflage cosmetics to cover pigmentation defects.^{14,15} Camouflaging principles are adapted from stage makeup texts, since many of the same techniques are employed.¹⁶ Fortunately, the cosmetics can be easily applied and removed, providing opportunity for experimentation and easy alteration of a bad result.

Pigmentation defects can be camouflaged by either applying an opaque cosmetic that allows none of the abnormal underlying skin tones to be appreciated or by applying foundations of complementary colors.¹⁷ For example, red pigmentation defects can be camouflaged by applying a green foundation, which is the complementary color to red. The blending of the red skin with the green foundation yields a brown tone, which can be readily covered by a more conventional facial foundation. Furthermore, yellow skin tones can be blended with a complementary colored purple foundation to also yield brown tones as is more easily covered by a conventional facial foundation.¹⁸ Skin areas that are lighter or darker than desired can be camouflaged by applying facial foundations with the appropriate amount of brown pigment to hide the defect. A good camouflage artist will generally purchase a color palette

from at least two different companies to provide the necessary mixture of cosmetic shades required to match a given patient's skin tone.¹⁹

Initially, a makeup base must be selected that is closest to the patient's natural skin color. Blending is usually necessary, but no more than three colors should be combined as this produces muddy final color quality. The underlying pigmentation problem counts as one color; so no more than two colors of facial foundation should be blended to achieve a good color match. Once the closest foundation color has been selected, it may be necessary to blend in yellow, if the individual has a sallow complexion, or reds, if the patient has a ruddy complexion, and so on. All facial tones should be represented in the final foundation blend if a good color match is to be obtained. Blending is usually done by applying a small amount of the makeup to the back of the hand. This provides a good surface for blending that can be easily held up to the face to evaluate the color match and also warms the product, allowing easier mixing and application.

The final foundation color mix is then dabbed, not rubbed, over the dyspigmentation area from the central face outward and into the hairline with blending over the ears and beneath the chin. The importance of dabbing and pushing the cosmetic into the skin cannot be overemphasized since this provides excellent adherence of the film to the skin, preventing removal by rubbing. Once the cosmetic has been adequately pressed into the skin, it should be allowed to dry untouched for at least 5 minutes. After drying of the film, the cosmetic must be set with an unpigmented finely ground talc-based powder to prevent smudging, improve wearability, provide waterproof characteristics, and impart a matte finish. Camouflaging makeups are designed to be worn with this powder and do not possess long wear characteristics without it. The powder should be pressed with a brush or sponge or the fingers into the foundation to physically bond the powder with the cosmetic film.

Lastly, a reddish powdered rouge is dusted over the central face, to include the central forehead, nose, and chin, as well as the upper cheeks to mimic natural increased reddish hues characteristic of this facial area. The high coverage camouflage cosmetic covers these facial landmarks, resulting in a flat, mask-like face if not properly highlighted. Other colored facial cosmetics, such as lipstick, eye shadow, eyeliner, mascara, and so on, are necessary to achieve an attractive final appearance.²⁰

Removal of facial camouflaging cosmetics can be challenging, requiring more than soap and water washing owing to the waterproof nature of the product. Most companies provide an oily cleanser for cosmetic removal that is applied on a cotton cosmetic pad. The pad should be saturated with the solution and then gently rubbed over the entire face. A greasy residue will be left behind because a water-in-oil emulsion is required to remove the waterproof cosmetic. The greasy residue can be removed with soap and water cleansing of the face. The cosmetic should only be worn when needed and definitely thoroughly removed

at bedtime.²¹ Never should new cosmetic be applied over old camouflaging cosmetic as the rub resistant and waterproof characteristics will be compromised. Only apply cosmetic to freshly washed skin.

ADVERSE REACTIONS TO CAMOUFLAGE COSMETICS

Camouflage cosmetics are generally used without difficulty once application and removal are mastered. A specially trained paramedical camouflage artist or esthetician can train the patient in blending and application of the makeup in two to three hourly sessions. The patient must then go home and practice to achieve a good result. The most common adverse reactions related to facial camouflage cosmetics are comedogenicity and acneogenicity. Most camouflage cosmetics contain a high oil concentration necessary for long wear and waterproof characteristics. These oils may cause comedone formation in predisposed individuals, but this is rare as most cosmetics are tested for comedogenicity. The oils most likely to cause comedogenicity are vegetable oils, but these oils can easily go rancid in formulation, so the oils utilized are mineral oil and silicone oil, neither of which causes comedone formation when used in cosmetic grade quality. If comedogenicity is suspected, use testing is best. This is accomplished by applying a small amount of the cosmetic to the upper lateral cheek for a 2- to 4-week period followed by dermatologic evaluation.

Camouflaging cosmetics are much more likely to be acneogenic than comedogenic. While the reaction to the cosmetic may appear like acne, the thick occlusive nature of the product may cause problems either at the follicular ostia or the sweat gland ostia. If the follicular ostia are occluded indeed, acne may occur, but more commonly, the sweat duct is occluded, resulting in miliaria rubra and pustulosa. It may be difficult to distinguish between these two conditions since they both appear as monotonous papules or pustules scattered across the face. The solution is to keep cool while wearing the cosmetic so that sebum and sweat do not accumulate under the thick waterproof cosmetic film.

Allergic contact dermatitis to camouflage cosmetics is rare since the formulation is generally fragrance-free with a low preservative concentration. It is possible, however, for both allergic and irritant contact dermatitis to occur with camouflage cosmetics. If a contact dermatitis is suspected, the cosmetics can be open or closed patch tested "as is." No dilutions or special preparations are necessary.

CAMOUFLAGE COSMETICS FOR SKIN OF COLOR

Pigmentation issues are more common and more challenging to camouflage in skin of color.²² It is estimated that there are 35 different hues for skin of color requiring tremendous color selection for camouflaging purposes.²³ This is compared to the seven basic colors required for Caucasian skin. Women of color traditionally wear facial foundations to blend uneven facial tones while fair-skinned individuals wear facial foundations to add color to the skin.²⁴ Greater emphasis is placed on skin of color

camouflaging foundations for dry skin, since pigmented skin is more subject to the ashy appearance of dry skin scale because of its higher rate of transepidermal water loss.^{25,26} This means that another skin hue is added to the camouflaging mix. Further, care must be taken to select camouflaging products that are nonirritating as worsening postinflammatory hyperpigmentation could create more camouflaging challenges.^{27,28}

The formulations and types of facial cosmetics available to patients with darker skin tones are the same as those formulated for lighter skin tones, which were previously discussed. Some cosmetic companies that traditionally cater to light-skinned customers have now enlarged their color selection to include darker skin tones. However, many new cosmetic companies are producing product lines specifically created for women of color.²⁹

The unique aspect of colored cosmetic formulation for darker skin tones is the blending of pigments with the underlying skin color. Fair-skinned individuals, with little underlying skin pigment, can select a colored cosmetic and expect it to look similar in the packaging and on the skin. However, women of color can expect the cosmetic to look entirely different in the package than on the skin as the cosmetic must blend with the numerous underlying skin hues.

To understand the principles of color blending and cosmetic camouflage for pigmentary abnormalities, it is necessary to discuss the artistic aspects of color in terms of value, intensity, and undertone.³⁰ The value of a color is a measure of its light reflectivity. Dark skin with blue/black or mahogany hues may appear deeper in color owing to the low value of these colors. Intensity refers to the brightness or dullness of a color. True colors, without the addition of white, brown or black pigments, tend to have higher intensity than mixed colors. For example, primary red has a greater intensity than brick red produced by the mixing of primary red with brown. This is an important concept in selecting facial foundations for dark skin, since too many pigments can leave the skin muddy appearing owing to reduced color intensity. Last, undertones are extremely important. The undertones account for the tremendous variation seen in skin of color. Red, yellow, or orange undertones are said to give the skin a warm appearance while blue, purple, or green undertones are said to give the skin a cool appearance. Based on an analysis of undertones, skin of color can be further classified as jet black, blue/black, purple/black, brown/red, bronze, honey, and so on. These hues must then be analyzed and balanced in skin of color to create a good cosmetic camouflage result.³¹

SUMMARY

Camouflage cosmetics may assist patients in better accepting their dyspigmentation issues and encourage compliance with treatment regimens. The cosmetic may actually be an important part of the treatment providing appearance improvement, photoprotection, and moisturization. The camouflage cosmetic can be worn over OTC and prescription pigment lightening preparations, keeping the

product in place and increasing efficacy by shielding the sun from causative UV radiation.³² While skill is required to achieve an optimal appearance result, the artistic application of camouflage cosmetics can restore self-confidence in patients undergoing dyspigmentation therapy.

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Sunscreens

PAULINE LECERF

The key role of ultraviolet (UV) radiation in the pathogenesis of the melasma is well established. UVB and UVA play a greater or lesser role, but some authors reported the impact of visible light on the pathogenesis of melasma a few years back.^{1,2}

UV LIGHT

UV radiation is usually divided into UVA (400–315 nm), UVB (315–290 nm), and UVC (290–200 nm). UVA has been further subdivided into UVA1 (400–340 nm) and UVA2 (340–315 nm). All the UVC and most of the UVB are absorbed by the oxygen and ozone in the earth's atmosphere. More than 95% of the sun's UV radiation that reaches the earth's surface is UVA.

The visible spectrum, used for general illumination, is defined as the portion of electromagnetic radiation visible to the human eye, which corresponds to wavelengths from 400 to 700 nm. The fact that visible light (UV-VL) can induce dark and relatively sustained pigmentation has a clinical implication on the treatment of photodermatoses.³

The depth of penetration of UV light within the skin is wavelength dependent. UVA readily reaches the dermis, including its deeper portions. UVB is absorbed in the epidermis, and only a small proportion reaches the upper dermis. UVC, if it reached the earth's surface, would be absorbed or reflected predominantly in the stratum corneum and in upper layers of the epidermis.

SUNSCREENS

The perfect sunscreen

- Protects against UVB and UVA.
- Offers protection from long-wave radiation (even into the visible range)
- Is long lasting
- Is water resistant
- Is cheap
- Is cosmetically acceptable (good sensorial properties)
- Allows dose compliance

Modern sunscreens were first developed during the 1940s with the primary aim of preventing sunburn. Today, sunscreens are also used to prevent other aspects of photodamage, including carcinogenesis and photoaging.

The measure of efficacy of sunscreens is designated the sun protection factor (SPF).

Mechanism

Sunscreens form a film or coating on the surface of the stratum corneum and attenuate radiation that would otherwise reach the living epidermis and dermis. The active agents in sunscreen products do this by either absorbing

or scattering the photons reaching the skin. Agents that scatter radiation are opaque particles of inorganic materials and are referred to as physical agents or sunblockers. Agents that absorb radiation are organic compounds, referred to as chemical agents or sunscreens. Scattering of radiation by inorganics is based on particle size, while chemical absorption is related to chemical structure. The photons scattered by the inorganic screens are reflected back out of the skin, whereas the energy absorbed by the organic agents is converted to nondamaging energy and dissipated primarily as heat. Many sunscreen products today contain combinations of both types of agents.

Because of the large particle size of the original preparations of inorganic agents, they were not deemed cosmetically acceptable, owing to their opaque appearance on the skin. Nowadays, these agents are formulated as micronized particles, resulting in products that are more cosmetically acceptable. However, such micronized inorganics actually act more like organic sunscreens, scattering as well as absorbing radiation to some extent.

Currently, most sunscreens contain a combination of two or more agents created to offer high levels of protection against both UVB and longer-wavelength radiation.^{4,5}

AGENTS

Organic screens

Para-aminobenzoic acid and derivatives

Padimate O (or octyl dimethyl PABA) is a PABA ester and one of the most common UVB absorbers found in sunscreens today. Both padimate O and its parent compound, PABA, are highly effective UVB absorbers. The latter causes staining of clothing and today is utilized infrequently.

Cinnamates

Octyl methoxycinnamate is a good UVB absorber but is not as potent as PABA and its esters. Presently, it is the most common sunscreen ingredient in the United States. Although an approved agent, cinoxate is currently not used in any sunscreens in the United States.

Salicylates

The salicylates are relatively weak UVB absorbers but do have the ability to stabilize other agents, thereby preventing photodegradation. Consequently, they are used in combination with other organics. This group includes octisalate, homosalate, and trolamine salicylate.

Benzophenones

Benzophenones are good UVA absorbers, although their effectiveness is primarily in the UVA2 range. Oxybenzone

is the most commonly used agent in this group and actually affords both UVB and UVA protection. Sulisobenzone and dioxybenzone have similar protective spectra but are infrequently utilized.

Other organic screens

Octocrylene is a commonly used UVB filter that is primarily employed to stabilize photolabile agents. Ensulizole is likewise a photostable UVB absorber. Avobenzone is an excellent UVA filter with absorption well into the UVA1 range but is very photolabile. It is combined with other agents that assist in stabilizing its protective ability. Menthyl anthranilate is a UVA filter with a maximum absorption in the UVA2 range, but its efficacy is relatively weak.

Inorganic screens

The physical blocking sunscreens (e.g., titanium dioxide) were used from the early days of sunscreen manufacturing, but, because of large particle size, were not cosmetically acceptable in high concentrations. Newer technology allowed for micronization of such particles, with an increase in transparency and therefore greater cosmetic acceptability.

The two major inorganic screens are titanium dioxide and zinc oxide. There are a few so-called chemical-free products that contain only inorganics, but usually these agents are combined with organic screens.

Other agents

Dihydroxyacetone is the compound most commonly used in sunless tanners. This agent, which when applied is colorless, binds to the stratum corneum and colors the skin to produce a tanned appearance. Although it has a very low SPF, it does offer protection from long-wave radiation (even into the visible range). Iron oxide offers protection across the UV spectrum and into the visible range and is used as a colorant in some products.⁴

Other “active” ingredients have been added to sunscreens, with claims of increasing efficacy of the finished products.⁶ The most popular of these are antioxidants, including vitamins E and C and green tea polyphenols, some of which have decreased UV-induced damage in *in vitro* and *in vivo* assays. However, factors including chemical structure, concentration, and stability in a finished product cannot be determined from package labels, so at this point it is impossible for the clinician and the consumer to judge efficacy.⁵

SIDE EFFECTS

Side effects from sunscreens include irritation (which is common) and allergy (which is rare).

The major adverse effects of sunscreens are minor skin irritation, which is common, and allergic contact dermatitis, which is rare. These reactions are usually attributed to ingredients in the base of the product, such as fragrance or preservatives. Presently, the organic compounds most often responsible for the rare instances of allergy or

photoallergy are oxybenzone and padimate O, and, less commonly, avobenzone.

Sunscreen usage and sun avoidance may lead to a decrease in vitamin D levels in some individuals; optimum vitamin D levels can be achieved with a healthy diet and supplements.⁵ This item is still debated.

USE OF SUNSCREENS AFTER TREATMENT FOR HYPERPIGMENTATION

Sunscreen after laser treatment

The use of the sunscreen after an ablative laser is still debated. For some authors, early application of sunscreen after ablative fractional skin resurfacing has increased the incidence of sensitization potential of sunscreen. Sunscreen use is recommended only 3 days after fractional ablative skin resurfacing to ensure the complete recovery of skin barrier and minimize the risk of sensitization.^{7,8}

For other authors, the use of broad-spectrum sunscreen with anti-inflammatory agents starting on the first day after ablative fractional skin resurfacing can decrease the incidence of PIH after laser treatment at 1-week postoperatively.⁹

Sunscreen and depigmenting cream

The use of 4% hydroquinone combined with 10% glycolic acid, antioxidants, and sunscreen in the treatment of melasma is safe and showed efficacy.¹⁰

UV-visible light (UV-VL) sunscreen enhances the depigmenting efficacy of hydroquinone compared with UV-only sunscreen in the treatment of melasma. These findings suggest a role for visible light in melasma pathogenesis.¹¹

Sunscreen after chemical peels

No official or evidence-based recommendations have been found in the literature. It is however advised to use sunscreen after peelings as sun eviction is recommended after these treatments. The initiation of sunscreen use after peeling may start immediately after 1 day for the superficial ones and after 3 days for the more deep ones once recovery of the barrier has been ensured.

Sunscreen as monotherapy for hyperpigmentation

Topical combination therapies were found to be more effective than monotherapy. Limitations of current literature include the heterogeneity of study designs, small sample sizes, and poor follow-up rates. Additional evidence for the effects and role of sunscreens is needed

Sunscreen as prevention after treatment for melasma

Some studies pointed out that broad-spectrum sunscreens protecting from UV radiation are useful in the management of melasma, but they failed to prevent relapses. The impact of the visible light on pigmentation is now demonstrated.³ However, using sunscreens effective against the entire visible light spectrum is almost impossible to use in daily practice.^{12–15}

Patients should try to integrate sunscreen use in their daily routine with frequent applications every 2 hours when the exposure to sun is more intense or at least as much as possible. Patient compliance might be improved if sufficient explanations on the role of both UV and visible light are given during consultation.

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THE PRINCIPLES OF MEDICAL THERAPY

Dimitris Rigopoulos and Alexander C. Katoulis

Introduction

The color of the skin is a sum of the amount and distribution of melanin within the various layers of the skin and their effect on light absorption. There are numerous processes that can modify skin color. While some can be considered normal, such as tanning after sun exposure, others can cause disfigurement, decreasing the quality of life for patients. Hyperpigmentation disorders include melasma, post-inflammatory hyperpigmentation (PIH), and hyperpigmentation caused by drugs or systemic diseases, among others. Identifying the causative agents for hyperpigmentation may be extremely valuable in choosing appropriate treatment regimens for patients. For example, the treatment choices, and prognosis, for a melasma appearing after pregnancy, are different from those for a hyperpigmentation caused by Addison's disease. A thorough medical history should be, therefore, obtained from patients.

The process of melanin formation

The major determinant of normal skin color is the activity of melanocytes, which refers to the quantity and quality of pigment production, not the density of melanocytes.¹ Melanocytes are neural crest-derived cells that migrate during embryogenesis to the epidermis and hair follicles. During adult life, each melanocyte is associated with approximately 30–40 keratinocytes, which surround it and receive the melanosomes that are produced by it. Each such complex is called an “epidermal melanin unit.”² Melanosomes are organelles, unique to melanocytes, in which melanin pigments are synthesized, deposited, and transported.³ The melanin biosynthetic pathway is a multifactorial process, in which tyrosinase is the key enzyme. Cutaneous pigmentation is a complex genetic trait, with more than 120 genes involved in its regulation, among which the melanocortin-1 receptor gene (MC1R) plays a key role.⁴ In general, tyrosine is the starting material through which all types of melanin are produced. Tyrosine is hydrolyzed by tyrosinase to DOPA, which is further metabolized to DOPAquinone. At this point, DOPAquinone may combine with cysteine to produce pheomelanin, a yellow red pigment, or can be further metabolized to DOPACHROME and then finally to eumelanin, a brown or black pigment, with the assistance of tyrosine-related protein (TYRP-1).⁵ The process of melaninogenesis is summarized in Figure 30.1.

Principles of therapy

The treatment of skin hyperpigmentation is based on three major pillars: sun protection, use of depigmenting formulations, and, finally, use of camouflage.⁶ The treatment of hyperpigmentation disorders includes topical formulations, chemical peels, lasers, and light sources. While no single therapy has proven to be of benefit to all patients as the sole therapy, combinations of modalities can be used to optimize management in difficult cases. First-line therapy of hyperpigmentation is topical treatment and includes therapies, such as hydroquinone, retinoids, chemical peels, and many other less well-studied compounds. Laser therapy may be used, but the evidence for improvement is mixed with a significant potential for worsening.⁷

MEDICAL THERAPY

Alexander C. Katoulis, Efthymia Soura,
and Antigone Alevizou

The aim of this section is to discuss the topical depigmenting agents.

Sunscreens and sun protection

The role of ultraviolet (UV) radiation in the appearance of melasma, skin aging, and the appearance of solar lentiginos has been studied extensively. Exposure to UV radiation induces secretion of various modulators from keratinocytes (such as endothelin 1, Interleukin-1, α -MSH, ACTH, or stem cell factors) that stimulate melanocytes to produce melanin. This UV-associated induction of melaninogenesis plays a major role in the appearance, or worsening, of melasma, which is, by definition, a disorder confined to sun-exposed areas.⁸ However, chronic sun exposure has also been associated with specific types of hyperpigmentation disorders, such as solar lentiginos. It has been demonstrated that although chronological aging is associated with a decrease in the total number of functional melanocytes, sun-exposed areas tend to maintain a higher level of functioning melanocytes compared to non-sun-exposed areas.⁵ In addition, a greater functional activity in older melanocytes after many years of cumulative sun exposure is also observed.⁵ In a recent study, it was reported that solar lentigine lesional skin was able to secrete higher levels of membrane-bound SCF, further promoting hyperpigmentation.⁹ The reason why only specific areas of sun-exposed surfaces of the skin become hyperpigmented in UV-damaged skin remains somewhat unidentified. It must be mentioned, though, that the mechanisms of skin aging, melaninogenesis, and solar skin damage are extremely complicated.

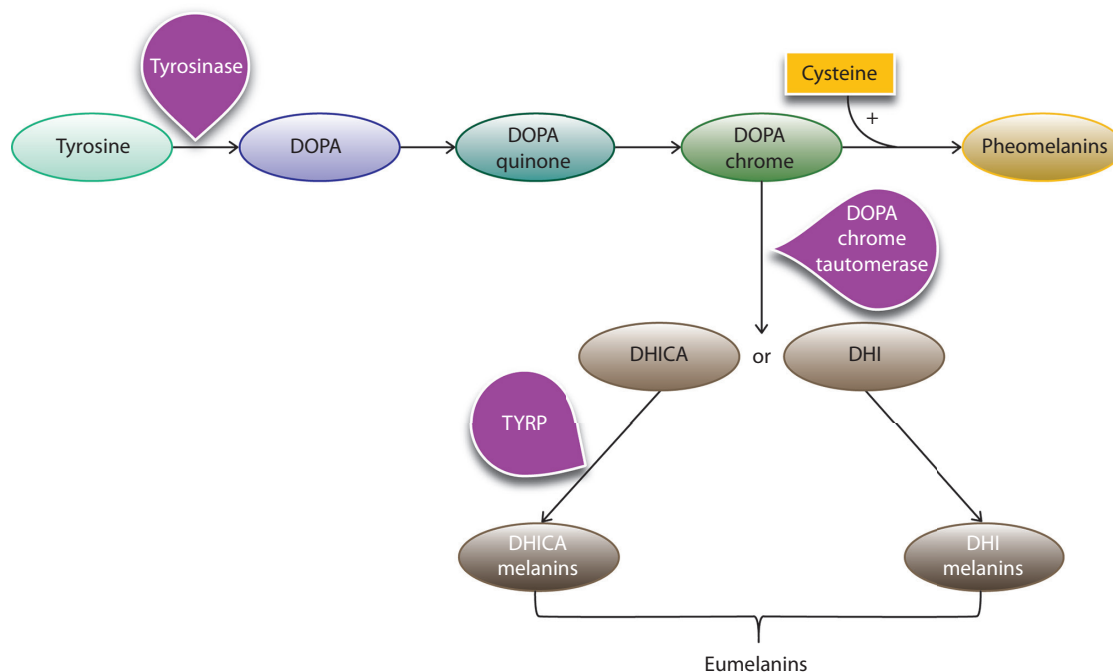


Figure 30.1 Process of melanogenesis.

Sunscreen agents

The importance of sun protection as a prophylaxis in hyperpigmentation disorders cannot be overstated. Highly protective sunscreens should be used concomitantly with depigmenting agents and is imperative that they should be considered an indispensable tool, not only in prevention, but also in the treatment of hyperpigmentation. In addition, patients should be educated on the use of daily broad-spectrum sunscreen and also on the importance of sun-protective measures, such as sun avoidance and protective clothing. This is particularly true for those with darker skin phototypes, who may not normally wear sunscreen, and although they are at higher risk of developing hyperpigmentation, they may not realize the darkening effects of UV irradiation.^{8,10,11}

The basic idea behind the use of sunscreens is that, when applied to the skin, they can form a protective UV radiation coating. In this way, ideally, the harmful effects of sun exposure on the epidermis and dermis could be attenuated. In modern sunscreens, this is achieved by compounds (filters) that are able to either absorb (also referred to as physical blockers or sunblocks) or scatter the photons that reach the skin (also referred to as chemical absorbers or sunscreens).¹²

The principal ingredients in sunscreens are usually aromatic molecules conjugated with carbonyl groups. This general structure allows the molecule to absorb high-energy UV rays and release the energy as lower-energy rays, thereby preventing the skin-damaging UV rays from reaching the skin. So, upon exposure to UV light, most of the ingredients (with the notable exception of avobenzone) do not undergo significant chemical change and are therefore able to retain UV-absorbing potency without significant photodegradation. Sunscreens may also contain

organic chemical compounds that absorb UV light; inorganic particulates that reflect, scatter, and absorb UV light (such as titanium dioxide, zinc oxide, or a combination of both); and organic particulates that mostly absorb light like organic chemical compounds, but contain multiple chromophores that may reflect and scatter a fraction of light like inorganic particulates and behave differently in formulations compared to organic chemical compounds. Most sunscreens contain combinations of different types of filters.^{12–15} A summary of FDA-allowable active ingredients in sunscreens can be found in Table 30.1.^{12–15}

Topical therapies

During the last few years, a number of topical therapies, including combination regimens, have become available for the treatment of hyperpigmentation.¹⁶ Most of these agents attempt to decrease pigmentation by interfering with various steps of the melaninogenesis process, such as decreasing the rate of melanocyte proliferation, inhibiting melanosome formation, or facilitating melanosome degradation.⁶ It is widely accepted that tyrosinase is a key component in the process of melanin production and is the major target for many of the agents that have been developed (Figure 30.1). Other possible therapeutic targets include L-DOPA, peroxidase, and copper (an important molecule that interacts at the enzyme's active site), among others.^{6,14} The main depigmenting agents that are currently available are summarized in Table 30.2.^{6,14,16}

Phenolic compounds

Hydroquinone

Hydroquinone is one of the oldest depigmenting agents and is still used as first-line agent, both as monotherapy and combined with other agents.¹⁷ Hydroquinone has

Table 30.1 Summary of FDA-allowable active ingredients in sunscreens.

UV-filter	Other names	Maximum concentration	Permitted in these countries	Results of safety testing	Absorption		
					UVB (290–320 nm)	UVA2 (320–340 nm)	UVA1 (340–400 nm)
Inorganic filters (“chemical absorbers”)							
<i>p</i> -Aminobenzoic acid	PABA	15% (EU: banned from sale to consumers from 8 October 2009)	USA, AUS	Protects against skin tumors in mice. Shown to increase DNA defects, however, and is now less commonly used	++		
Padimate O	OD-PABA, octyldimethyl-PABA, σ-PABA	8% (EU, USA, AUS), 10% (JP) (Not currently supported in EU and may be delisted)	EU, USA, AUS, JP		++		
Phenylbenzimidazole sulfonic acid	Ensulizole, Eusolex 232, PBSA, Parsol HS	4% (US, AUS), 8% (EU), 3% (JP)	EU, USA, AUS, JP	Genotoxic in bacteria	++		
Cinoxate	2-Ethoxyethyl <i>p</i> -methoxycinnamate	3% (US), 6% (AUS)	USA, AUS		++		
Dioxybenzone	Benzophenone-8	3%	USA, AUS		++	+	
Oxybenzone	Benzophenone-3, Eusolex 4360, Escalol 567	6% (US), 10% (AUS, EU), 5% (JP)	EU, USA, AUS, JP		++	++	
Homosalate	Homomethyl salicylate, HMS	10% (EU, JP), 15% (US, AUS)	EU, USA, AUS, JP				
Menthyl anthranilate	Meradimate	5%	USA, AUS				
Octocrylene	Eusolex OCR, 2-cyano-3,3-diphenyl acrylic acid, 2-ethylhexylester	10%	EU, USA, AUS, JP	Increases ROS	++		
Octyl methoxycinnamate	Octinoxate, EMC, OMC, ethylhexyl methoxycinnamate, Escalol 557, 2-ethylhexyl-paramethoxycinnamate, Parsol MCX	7.5% (US), 10% (EU, AUS), 20% (JP)	EU, USA, AUS, JP				
Octyl salicylate	Octisalate, 2-ethylhexyl salicylate, Escalol 587,	5% (EU, USA, AUS), 10% (JP)	EU, USA, AUS, JP				
Sulisobenzone	2-Hydroxy-4-methoxybenzophenone-5-sulfonic acid, 3-benzoyl-4-hydroxy-6-methoxybenzene sulfonic acid, benzophenone-4, Escalol 577	5% (EU), 10% (US, AUS, JP)	EU, USA, AUS, JP			++	+
Trolamine salicylate	Triethanolamine salicylate	12%	USA, AUS				
Avobenzone	1-(4-methoxyphenyl)-3-(4-tert-butyl phenyl) propane-1,3-dione, butyl methoxy dibenzoylmethane, BMDBM, Parsol 1789, Eusolex 9020	3% (US), 5% (EU, AUS), 10% (JP)	EU, USA, AUS, JP	Not available		++	++

(Continued)

Table 30.1 (Continued) Summary of FDA-allowable active ingredients in sunscreens.

UV-filter	Other names	Maximum concentration	Permitted in these countries	Results of safety testing	Absorption		
					UVB (290–320 nm)	UVA2 (320–340 nm)	UVA1 (340–400 nm)
Ecamsule	Mexoryl SX, terephthalylidene dicamphor sulfonic acid	10%	EU, AUS (US: approved in certain formulations up to 3% via New Drug Application [NDA] route)	Protects against skin tumors in mice		++	++
Inorganic filters ("physical blockers")							
Titanium dioxide	CI77891	25% (No limit JP)	EU, USA, AUS, JP	Protects from visible light	++	++	++
Zinc oxide		25% (US) (AUS, JP: no limit)	USA, AUS, JP	Protects against skin tumors in mice Protects from visible light	++	++	++

Source: Balogh TS et al., *An Bras Dermatol*, 86(4):732–42, 2011; Kullavanijaya P and Lim HW, *J Am Acad Dermatol*, 52(6):937–58, quiz 959–62, 2005; Sheth VM and Pandya AG, *J Am Acad Dermatol*, 65(4):699–714, quiz 715, 2011; Lim HW et al., *J Am Acad Dermatol*, 44(3):505–8, 2001.

been used for the treatment of melasma for more than 50 years, with the first reported clinical trial performed in 1965.¹⁸ Since then, a number of randomized clinical trials have confirmed the efficacy of hydroquinone in the treatment of skin hyperpigmentations.¹⁶

Hydroquinone is a hydroxyphenolic chemical that is thought to act by inhibiting tyrosinase, possibly by binding to the enzyme or by interaction with copper molecules

at the enzyme's active site. The inhibition of tyrosinase leads to altered melanosome formation and increased melanosome degradation¹⁹ and perhaps even to the inhibition of DNA and RNA synthesis.²⁰ Additionally, cytotoxic metabolites of hydroquinone may cause interference with melanocyte function and viability.

In general, hydroquinone can be applied either in cream form or as an alcohol-based solution. Concentrations

Table 30.2 Summary of depigmenting agents and their mode of action.

Proposed mechanism of action	Compound	
	Plant derivatives	Non-plant derivatives
Competitive tyrosinase inhibition	Azelaic acid Arbutin and deoxyarbutin Aloesin Kojic acid Flavonoids	Hydroquinone Mequinol Gentisic acid Glutathione
Non-competitive tyrosinase inhibition	Glabiridin Resveratrol Polyphenolic compounds	N-acetyl-glucosamine Hagin
Stimulation of keratinocyte turnover		Retinoids
Reduction in melanosome transfer	Soybean trypsin inhibitor	Retinoids
Interaction with copper	Kojic acid Ascorbic acid Ellagic acid	
Inhibition of melanosome maturation	Arbutin and deoxyarbutin	
Inhibition of protease-activated receptor 2	Soybean trypsin inhibitor	
Inhibition of plasmin	Traxenamic acid	
Inhibition of α -MSH-induced melanin production	Undecylenoyl phenylalanine	

Source: Shankar K et al., *Dermatol Ther (Heidelb)*, 4(2):165–86, 2014; Sheth VM and Pandya AG, *J Am Acad Dermatol*, 65(4):699–714, quiz 715, 2011; Jutley GS et al., *J Am Acad Dermatol*, 70(2):369–73, 2014.

vary from 2% to 5%, although in some cases the use of higher concentrations has also been reported (<10%). In a study by Verallo-Rowell et al., it was reported that when hydroquinone is used in low concentrations (2%), it shows similar or even inferior efficacy to other depigmenting agents (e.g., 20% azelaic acid).²¹ Similarly, the use of concentrations >5% may be associated with a high risk of various adverse events, including ochronosis, for darker-skinned patients, contact dermatitis, or even nail discolorations.^{14,22} The optimal concentration of hydroquinone as monotherapy has been determined to be 3%–4% in terms of safety and tolerability.¹⁶ The combination of hydroquinone, tretinoin, and steroid seems more effective than any of the agents in a dual-combination cream.²³ The strongest clinical evidence exists for a fixed triple-combination therapy of hydroquinone 4%, retinoic acid 0.05%, and fluocinolone acetonide 0.01%, known as the Kligman formula.²³ Those data are confirmed by a recent systemic meta-analysis in the Cochrane database that has reported that triple-combination cream was significantly more effective at improving melasma not only when compared to hydroquinone alone (risk ratio [RR], 1.58; 95% confidence interval [CI], 1.26 to 1.97) but also when compared to various dual-combination treatments such as tretinoin and hydroquinone (RR, 2.75; 95% CI, 1.59 to 4.74), tretinoin and fluocinolone acetonide (RR, 14.00; 95% CI, 4.43 to 44.25), and hydroquinone and fluocinolone acetonide (RR, 10.50; 95% CI, 3.85 to 28.60).²⁴ It is recommended that the preparations are applied uniformly and once or twice daily to the affected area. The optimal duration of treatment is not yet defined, with some authors suggesting that if no improvement is seen after 2 months of therapy, treatment should be discontinued. However, it is widely accepted that pigment lightening, when hydroquinone is used, usually becomes apparent after 5–7 weeks of therapy. In general, treatment with hydroquinone should be continued for at least 3 months and up to 1 year.²⁵

Hydroquinone is considered a safe and effective treatment when used at concentrations of less than 4%.²² Mild skin irritation, itching, burning, stinging, appearance of contact-type dermatitis, and phototoxicity, followed by secondary post-inflammatory hyperpigmentation (PIH), have all been associated with topical application of hydroquinone. Such adverse events tend to be more frequent with formulations containing higher concentrations of hydroquinone. Chronic use of high concentrations of hydroquinone (≥5%) has been reported to produce exogenous ochronosis, a bluish-gray discoloration, and colloid milium, especially in patients with darker skin phototypes.^{14,26} There has been wide concern over the use of hydroquinone in over-the-counter products. This concern mainly stemmed from the fact that these products were readily available to patients without a doctor's prescription, while most of them were not appropriately tested with clinical trials for their safety. As a result, a number of patients experienced adverse events such as ochronosis, irritation, and localized vitiligo, with most of these side effects being a result of misuse, excessive use, and

the application of multiple preparations.^{27,28} This has led to the banning of the free use of hydroquinone as a cosmetic ingredient in several European countries, in which it can now only be used as a prescription drug.¹⁴ Another concern regarding hydroquinone use is a potential association with carcinogenicity. Most specifically, hydroquinone, when administered orally, is metabolized by the liver to produce benzene derivatives, which are known carcinogens.²⁹ These derivatives are proposed to cause bone marrow toxicity and exert an antiapoptotic effect. However, topically applied hydroquinone bypasses the liver initially and is mainly metabolized via water-soluble, renally excreted molecules.²⁹ Another concern is the risk of developing renal adenomas because of potentially toxic metabolites, but topical hydroquinone has not been shown to have renal toxicity. In addition, there have been no reports to date of skin or internal organ malignancies occurring in humans as a result of topical hydroquinone application, despite being in use since the middle of the twentieth century.^{27,28}

Although it is maintained that the risk of developing a malignancy attributed to the topical use of hydroquinone is only theoretical and that the possibility or the appearance of an adverse event, such as ochronosis, is exceedingly low, topical preparations of hydroquinone should be administered as prescription drugs and under the supervision of a trained physician.²⁷ In addition, it must be mentioned that hydroquinone is a class C drug and therefore should not be used during pregnancy.

Mequinol

Mequinol is a derivative of hydroquinone that belongs to the category of phenolic compounds. It acts as a substrate of tyrosinase, competitively inhibiting melanin production without exerting any toxicity on melanocytes.³⁰

Mequinol has been used in combination with tretinoin for the treatment of solar lentigines and melasma. A number of studies have shown promising results of the 0.01% tretinoin–2% mequinol combination, although more controlled clinical trials are needed to establish its place in the management of hyperpigmentation.³¹ In a small case series, which included five male patients, a 2% mequinol–0.01% tretinoin solution was used successfully in the treatment of melasma.³² In addition, the combination of 2% mequinol–0.01% tretinoin solution was also reported to be superior to a 3% hydroquinone solution when used for the treatment of solar lentigines of the arms and face.³³ Similar results were reported by other authors as well.^{34,35}

Overall, mequinol is considered safe, with most common side effects being irritation (probably associated with sun exposure since it improves after application of a sunscreen), burning, stinging, tingling, desquamation, pruritus, halo hypopigmentation, and depigmentation both locally and at distant sites.³² The mequinol combination with isotretinoin is considered an X class drug and should be strictly avoided during pregnancy. In addition, because of a possible photosensitizing effect, it should be used with caution in patients taking any type of photosensitizing medications.³²

Retinoids

During the last few years, a number of retinoids, such as isotretinoin, tazarotene, and adapalene, have been used in the treatment of various hyperpigmentation disorders, either as monotherapy or in combination with other depigmenting agents.³⁶

The exact mechanism of action of retinoids, when used as depigmenting agents, is not yet fully understood. This could be, in part, attributed to the fact that different types of retinoids exert their actions on different types of retinoid receptors. For instance, isotretinoin itself does not bind to retinoic acid receptors (RARs), but may instead act largely as a prodrug for all-*trans* retinoic acid (although its metabolites may also play a significant role).³⁷ All-*trans* retinoic acid (tretinoin) may be able to increase epidermal cell turnover and has been shown to exhibit an inhibitory effect on tyrosinase, TYRP-1, and TYRP-2 (even after UVB exposure).³⁸ However, tretinoin has been known to influence the expression of more than 500 genes, out of which only 27 have been studied.^{37,39} It should not be, therefore, considered strange that it has demonstrated a bimodal function, by stimulating (induces melanocyte proliferation) and inhibiting (increases apoptosis of mature melanocytes) melaninogenesis at the same time in murine models.³⁶ Adapalene, on the other hand, exhibits a high affinity toward RAR β and RAR γ and can reach high concentrations in the pilosebaceous unit. The RAR–adapalene complex is able to bind to the retinoid X receptor and therefore modulate keratinization and inflammation.⁴⁰

Tretinoin

The efficacy of tretinoin in the treatment of hyperpigmentation has been investigated in several randomized clinical trials. In a study that included 38 female patients with facial melasma, it was shown that the application of 0.1% tretinoin cream was associated with significant improvement, observed after 24 weeks of treatment.⁴¹ Acceptable results were reported in another study where a similar cream was administered in 30 African–American patients with melasma. A 32% improvement in the Melasma Area and Severity Index (MASI) score was observed after 40 weeks of treatment.⁴² However, in a study that included 30 Thai patients, the application of 0.05% isotretinoin gel was not associated with a statistically important improvement of melasma when compared to simple sunscreen use after 40 weeks of treatment.⁴³ Tretinoin has also been evaluated in the treatment of solar lentigines (and/or solar elastosis) and PIH. A recent study that included 19 patients who were treated with tretinoin cream 0.02% for 52 weeks demonstrated a beneficial effect in wrinkling, tactile roughness, and mottled hyperpigmentation as well as in lentigines, evident from the 6th month of treatment.⁴⁴ Similar results were reported in another trial where 0.1% tretinoin cream was administered in 60 patients for the treatment of solar lentigines for a duration of 10 months.⁴⁵ In 83% of patients, a lightening effect of the lesions was reported, while there

were no recurrences observed after treatment cessation, during the 6-month follow-up period.⁴⁵ Finally, tretinoin was found to be beneficial in the treatment of PIH in a small trial that included 65 patients with PIH resulting from acne. After tretinoin 0.1% cream was administered for 40 weeks, it was observed that significantly more patients had lighter facial lesions in the tretinoin group compared to the nontreatment group.⁴⁶

Given the longer treatment time needed to see a clinical benefit and the frequent occurrence of irritation, tretinoin may not be very useful as monotherapy for melasma and solar lentigines, while no specific recommendations can be made for the treatment of PIH.¹⁴ However, it has been found to be extremely beneficial when used in combination with other depigmenting agents and especially with hydroquinone and fluocinolone acetonide.¹⁶ As a matter of fact, tretinoin, when used in combination, acts synergistically by increasing the absorption of other depigmenting agents, while still maintaining its own depigmenting properties. It is therefore not unreasonable that it is considered a main ingredient for many combination therapies in melasma.^{47–50} Tretinoin is available in three forms: gel, cream, and liquid, at strengths ranging from 0.01% to 0.1%.³⁶

The most common side effects of tretinoin include a retinoid dermatitis characterized by burning or stinging, erythema, scaling, and dry skin.^{41,42} Given that tretinoin can be irritating, the dose must be adjusted to prevent inflammation. This inflammation may cause hyperpigmentation, especially in those with dark skin. Fortunately, most adverse effects are reversible on discontinuation of therapy, although the hyperpigmentation/hypopigmentation may persist for many months. Cutaneous reactions are predominantly moderate and only few have been reported to be severe. They are mostly limited to erythema, peeling, or both of the area of application. Generally, side effects are characterized as mild and result in no patient withdrawals.^{41–43} Special care should be taken when topical tretinoin is administered in patients with possible hypersensitivity to retinoids. In addition, patients should be warned that tretinoin may have a photosensitizing effect. The drug is categorized as class X and should not be administered during pregnancy.

Adapalene

Adapalene, as mentioned previously, is a synthetic retinoid that exhibits a high affinity toward RAR β and RAR γ and, by acting in a more targeted manner compared to tretinoin, is associated with a milder adverse event profile.⁴⁰ In a randomized split-face study that included 30 Indian females, no difference in efficacy was observed between 0.05% isotretinoin and 0.1% adapalene in the treatment of melasma, while adapalene was considered better tolerated.⁵¹ Adapalene has also been found to be moderately effective in the treatment of solar lentigines. A study that included 90 patients evaluated the efficacy and safety of adapalene gel 0.1% and 0.3% in the treatment of actinic keratosis and solar lentigines. It was reported that 57% and 59% of patients receiving adapalene 0.1% and 0.3% gel, respectively, exhibited lighter

lesions compared to only 36% of patients receiving vehicle-only, after 9 months of treatment.⁵² The reported adverse events were mild and/or moderate and included erythema, peeling, dryness, burning, and pruritus.⁵²

In general, there are few data available from clinical trials regarding the efficacy and safety of adapalene in the treatment of hyperpigmentation. However, existing data indicate that patients using adapalene, alone, may exhibit moderate clinical improvement, while presenting with fewer side effects.¹⁴

Tazarotene

Tazarotene is a retinoid prodrug that belongs to the family of acetylenic class of retinoids. The active form of tazarotene, tazarotenic acid, is able to bind to all three members of the RAR family—RAR α , RAR β , and RAR γ —but shows relative selectivity for RAR β and RAR γ , which are found in abundance on the skin.⁵³ Recently, a 0.1% concentration was approved for use in patients with acne, while the potential benefits of its use in hyperpigmentation disorders were also explored.^{36,53}

Tazarotene cream (0.1%) was assessed in a 6-month randomized controlled study that included 563 patients. It was reported that once-daily application of tazarotene was associated with a clinical improvement in solar lentigines after 6 months of treatment.⁵⁴ In addition, in another study, no statistically significant differences in clinical response of solar lentigines were observed between the patients treated with tazarotene cream 0.1% or tretinoin 0.05% cream.⁵⁵ However, it was reported that all significant differences between groups were in favor of tazarotene. These included fine and coarse wrinkling and hyperpigmentation.⁵⁵ A study that included 74 patients with darker skin phototypes demonstrated that once-daily application of tazarotene 0.1% cream was associated with significant reduction of post-acne PIH compared to treatment with vehicle cream after 18 weeks of treatment.⁵⁶

Adverse events associated with the use of tazarotene include topical irritation, dryness, erythema, and exfoliation, while in some cases stinging or burning sensation has also been observed. The drug is considered category X and should not be administered during pregnancy.

Corticosteroids

Corticosteroids have been used in combination with various depigmenting agents for numerous years. The rationale behind their use is that they may exert antimetabolic effects, which could result in decreased epidermal turnover.⁵⁷ Some authors have also suggested that corticosteroids may directly affect the synthesis of melanin, although this possibility remains to be investigated. Since chemical mediators of inflammation, such as prostaglandins and leukotrienes, affect the function of melanocytes, it would not be impossible that corticosteroids might alter melanocyte function by inhibiting prostaglandin or cytokine production.⁵⁸ In addition, corticosteroids, when used in combination therapies, besides exhibiting a mild depigmenting potential, also play an important role by

suppressing the inflammation caused by the retinoids.⁵⁸ On the other hand, retinoids mitigate the possible atrophy associated with the long-term corticosteroid use.¹⁴

In general, corticosteroids have not been found to be very effective in the treatment of hyperpigmentation when used as monotherapy. In a small trial that included 15 patients, it was reported that treatment with betamethasone 17-valerate was associated with clinical improvement after 3 months of treatment in patients with melasma or secondary hyperpigmentation.⁵⁹ In another study, topical application of clobetasol propionate (0.05%) has been found to cause transient fading of pigmentation (lasting only a few weeks) after 2 weeks of treatment.¹⁷ However, these results are contradicted by early studies performed by Kligman and Willis, where topical dexamethasone as monotherapy produced little depigmentation even after 3 months of therapy.⁵⁷ In a recent study, intralesional triamcinolone (4 mg/cc and 5-mm intervals) was compared to combination therapy (hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1%) in the treatment of melasma.⁶⁰ It was reported that the patients receiving the microinjection therapy exhibited higher changes in MASI scores compared to the patients receiving the combination therapy after 8 weeks of treatment.⁶⁰ Various corticosteroids have been used in triple-combination formulations. These include dexamethasone, hydrocortisone 1%, mometasone, and fluorinated steroids (such as 0.01% fluocinolone acetonide and fluticasone).⁶

The topical use of corticosteroids has been associated with various adverse events. Steroid-induced acne is not uncommon and is characterized by the appearance of a rosacea-like eruption with persistent erythema, pustules, and papules, distributed in a centropacial manner. This type of acne may flare if the corticosteroids are withdrawn abruptly, but usually improves after 1–3 months. Perioral dermatitis, seen predominately in adult women, is also possible. Another possible adverse event of topical corticosteroids, which are often used to treat allergic disorders, is allergic contact dermatitis. This adverse event has been observed with most topical corticosteroids.⁶¹ Skin atrophy may also be observed after long-term use. The skin becomes thinner and underlying vessels may become apparent. Telangiectasias may also be observed.⁶¹ For instance, in a study by Kanwar et al., a number of patients had to cease treatment after 4 weeks of treatment with clobetasol propionate 0.05% owing to local atrophy and appearance of telangiectasias.¹⁷ At this point, corticosteroids are not recommended as monotherapy for the treatment of melasma. However, when used in combination therapy, fluorinated steroids have been found to be superior to nonfluorinated steroids, both in efficacy and in safety.⁶

Combination therapies and galenic formulations

Although numerous agents have been used as monotherapy for the treatment of melasma and other types of hyperpigmentation disorders, no single agent has been proven to be highly efficacious. For this reason, a number of combination treatments have also been investigated.

Hydroquinone has been used in various concentrations as a key component of combination therapies. Such combinations include hydroquinone 5%, tretinoin 0.1%, and dexamethasone acetate 0.1%; hydroquinone 2%, tretinoin 0.05%, and betamethasone valerate 0.1%; or hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%. Some of these regimens have been described in various previous sections of this chapter. The 5% hydroquinone combination has been originally introduced by Kligman and Willis and has been shown to be effective in the treatment of melasma. In the original paper by Kligman et al., the regimen was applied for 5 to 7 weeks on affected skin of adult male African-American patients. It was reported that melasma, ephelides, and PIH improved after treatment.⁶² Similarly, positive results have been reported in other, more recent papers; however, it must be mentioned that this particular combination is frequently associated with marked skin irritation (erythema and peeling).⁶³ The efficacy of a smaller hydroquinone concentration (2%) triple-combination therapy was also investigated. The rationale behind the decrease in HQ concentration is the avoidance of skin irritation, while maintaining an adequate depigmenting effect. This particular combination therapy has not been proven to be very efficacious in the treatment of hyperpigmentations, but may present an appropriate choice for patients with darker skin phototypes. In a recent study involving patients from India (Fitzpatrick type IV–VI), it was reported that 36.7% of patients believed that their appearance had improved. However, in this study, 1% concentration mometasone was used and steroid side effects were observed in 43.3% of patients.⁶⁴ At this point, the most effective triple-combination therapy is considered to be the “modified” Kligman regimen, which contains a 4% HQ concentration. Taylor et al., in a study that included 641 patients, compared the efficacy of a triple-combination cream (fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%) applied for 8 weeks to that of various double-combination regimens, also applied for a duration of 8 weeks. These included a hydroquinone 4% and tretinoin 0.05% combination, a fluocinolone acetonide 0.01% and tretinoin 0.05% combination, and a fluocinolone acetonide 0.01% and hydroquinone 4% combination. The results of the study demonstrated superiority of the triple-combination therapy over the double-combination therapies, with 26.1% and 4.6% of patients experiencing complete clearance. Additionally, 70% of patients in the RA + HQ + FA arm and 30% of patients in the dual-combination arm exhibited 75% reduction in melasma/pigmentation severity, respectively.²³ Similar results were reported by numerous other clinical trials.^{6,65} The most common adverse reactions seen with all treatment groups were erythema, skin peeling, burning, or stinging sensation. Long-term safety and efficacy data, as reported by the Cochrane system database, have identified the 4% HQ combination therapy as the most efficacious treatment for melasma until this point.¹⁶ (Also see section on hydroquinone.)

The efficacy of HQ 4% concentration in combination with a sunscreen has also been investigated. More specifically, in a study by Ennes et al., the efficacy of 4% HQ combined with two sunscreens (SPF-15) in a single cream, and applied for 12 weeks, was compared to that of application of the two sunscreens only, in 48 patients. It was reported that the combination cream showed clinical superior results to that of the sunscreen-only cream; however, it was not stated clearly which parameters were assessed in patients and therefore results may be equivocal.⁶⁶ Hydroquinone has also been investigated in combination with glycolic acid (GA). In a study by Guevara et al., the combination of 4% hydroquinone, 10% buffered GA, vitamin C, vitamin E, and sunscreen, applied twice daily, was compared to sunscreen use only. It was reported that 75% of patients on the treatment arm improved, compared to only 13% of patients who only applied sunscreen. There were no specific serious adverse events.⁶⁷ The combination of hydroquinone with GA has been investigated in other clinical trials.⁶⁸ For instance, Lim et al. reported that the combination of 2% HQ, 10% GA, and 2% kojic acid (KA) was effective in the treatment of melasma. Moreover, this combination therapy was compared to the combination of 2% HQ and 10% GA and was found to be superior.⁶⁹ Combinations of depigmenting agents with a variety of chemical peels have also been investigated. Selected trials will be mentioned in corresponding sections of this chapter.

Combinations of various depigmenting agents have also been investigated in other types of hyperpigmentations besides melasma. For instance, Yoshimura et al. reported that in a study conducted in 136 Oriental patients that received a 0.1% or 0.4% retinoic acid plus 5% HQ formulation, improvement of solar lentigines was observed in 82.2% of patients after 8 weeks of treatment.⁷⁰ Similarly, in a study that included 216 patients with solar lentigines, the combination of mequinol 2% and tretinoin 0.01% was found to be associated with better results compared to 3% HQ solution, after 12 weeks of treatment.^{33,71}

Azelaic acid

Azelaic acid (AA) is a naturally occurring saturated dicarboxylic acid that acts as a reversible competitive inhibitor of tyrosinase. In general, its effect on tyrosinase is considered weak, but it is believed that AA may also be able to decrease melanocytic proliferation and exert cytotoxic effects on abnormal melanocytes by interfering with mitochondrial respiration and DNA synthesis.^{14,72}

The efficacy of AA in the treatment of melasma has been investigated in a series of clinical trials. Recently, Farshi reported that the improvement in MASI score was comparable between two groups of patients who received treatment with either 20% AA or HQ 4% (3.8 ± 2.8 and 6.2 ± 3.6 , respectively) after 6 months of twice-daily application.⁷³ Similar results were reported by other trials as well. In a previous study by Baliña et al. that included 329 female patients, it was observed that 71.9% of those in the hydroquinone 4% group showed marked improvement versus 64.8% in the AA 20% group, after 24 weeks of twice-daily

application.⁷⁴ Sivayathorn et al. compared the efficacy of AA 20% with that of HQ 2%. In this study (340 patients), it was demonstrated that the effect of AA 20% was comparable to that of HQ 2%, with a higher number of patients in the AA group achieving more than 50% improvement from baseline.⁷⁵ AA has also been used as a component in various combination creams. In a recent study by Mazurek et al., three different combination regimens containing AA were compared. The creams were applied for 24 weeks, and the efficacy was evaluated after assessing pigmentation, erythema, and the level of hydration and elasticity. It was reported that a combination containing 20% AA and mandelic acid, phytic acid, 4N-butyl resorcinol, and ferulic acid was the most effective treatment. However, it must be mentioned that in this study, there was no control arm with patients receiving AA only.⁷⁶ In general, these results support the fact that AA is an effective treatment for melasma and can be considered for patients that are intolerant to HQ.

AA has been found to be rather ineffective in the treatment of solar lentigines. In a study with 50 women of Southeast Asian origin, a formulation of either 20% AA or 5% ascorbyl glucosamine, 1% KA, and alpha-hydroxyacid esters were administered for up to 2–3 months, twice daily with disappointing results.⁷⁷ However, AA may be beneficial in the treatment of acne-associated PIH, especially in patients of color.^{78,79}

The adverse events associated with the use of AA are generally mild. These include mainly pruritus, mild erythema, scaling, and burning. AA can be used in conjunction with retinoids, and is considered pregnancy class B.¹⁴

Kojic acid

KA is a tyrosinase inhibitor that acts mainly by chelating copper at the enzyme's active site. It is an acid naturally produced by *Aspergillus oryzae* and *Penicillium* spp. and is used widely as a depigmenting agent in numerous formulations. Recently, it was reported that it may also upregulate interleukin-6 in keratinocytes, thus inhibiting melanin production.¹⁴

KA can be found in concentrations ranging from 1% to 4% and is a component in numerous combination regimens. Various studies have shown that when used as monotherapy in the treatment of melasma, it produces modest results.⁶ Deo et al. compared the efficacy of 1% KA to that of KA 1% and HQ 2%, KA 1% and betamethasone valerate 0.1%, and a combination of all three agents, applied once daily for 12 weeks, in a study that included 80 patients with melasma. It was demonstrated that the combination of KA and HQ was more efficacious. No direct comparison between KA and HQ as monotherapies was made in this study.⁸⁰ In another study, the efficacy of HQ 4% and a combination of 0.75% KA and vitamin C was compared. After 12 weeks, HQ 4% was reported to be superior to the combination regimen.⁸¹ However, KA may improve the efficacy of combination depigmenting regimens when used as a component. In a study where the efficacy of a gel containing 2% KA, 10%

GA, and 2% HQ was compared to that of a gel containing only HQ and GA, the three-agent combination was found to be associated with better results.⁶⁹ There are very limited data regarding the value of KA in the treatment of other types of hyperpigmentations besides melasma. In general, KA may be considered as an alternative treatment for patients not responding to treatments with HQ or AA. It must be mentioned, though, that KA is a known sensitizer and its use has been strongly associated with adverse events such as burning sensation, erythema, and contact dermatitis. Therefore, it must be used with caution.^{6,14,30}

Ascorbic acid

Ascorbic acid (AsA) is also known as vitamin C. Similarly to KA, it acts by chelating copper at tyrosinase's active site, thus inhibiting the enzyme's function. In addition, it reduces dopaquinone by blocking dihydro-chinindol-2-carboxylic acid oxidation.^{14,30}

In general, AsA has demonstrated moderate efficacy in the treatment of melasma when used as monotherapy. In a study by Espinal-Perez et al., it was reported that HQ 4% exhibited better efficacy compared to that of 5% AsA after 16 weeks of treatment.⁸² In addition, it must be mentioned that this is a highly unstable molecule that is rapidly oxidized and therefore is better used in combination with other depigmenting agents such as GA, KA licorice extracts, or soy.¹⁴ In a recent study, L-AsA 25% was combined with a chemical penetration enhancer in order to increase efficacy and stability. The results were favorable as a significant decrease was noted in the degree of pigmentation, as evaluated by MASI and mexameter scores, after 16 weeks of treatment.⁸³ There are very limited data regarding the value of AsA in the treatment of other types of hyperpigmentations besides melasma.

AsA is associated with mild adverse events and is overall considered safe. Therefore, it can be considered as an alternative therapy in patients who cannot tolerate hydroquinone.

Undecylenoyl phenylalanine

Undecylenoyl phenylalanine (UP) is a new depigmenting agent that acts in a distinct way compared to other depigmenting agents. UP does not inhibit tyrosinase but rather acts by stimulating α -melanocyte-stimulating hormone (α -MSH) and as a β -adrenergic receptor (β -ADR) antagonist.⁸⁴ Various studies have investigated the efficacy of UP in the treatment of melasma and other hyperpigmentation disorders. Katoulis et al. has reported the beneficial effects of treatment with UP in two different studies. In the first study, 36 patients with solar lentigines received UP 2% twice daily for 12 weeks. It was reported that 80% of patients were satisfied with the results, as most achieved partial responses to treatment.⁸⁵ In the second study, 40 patients with melasma received treatment with topical 2% UP or vehicle cream twice daily for 12 weeks, and it was reported that 85% of patients receiving treatment with UP showed improvement of lesions compared

to only 23% of patients receiving vehicle cream.⁸⁶ More studies are needed in order to fully evaluate the role of UP in melasma; however, these limited data are encouraging.

Arbutin

Arbutin is considered as one of the most widely prescribed lightening agents and is most commonly used as a component in combination regimens. Arbutin and deoxyarbutin are β -D-glucopyranoside derivatives of hydroquinone. Arbutin is a naturally derived compound, extracted from dry leaves of various plants such as bearberry, blueberry, and cranberry plants and pear trees.^{30,87} Deoxyarbutin is a synthetic derivative of hydroquinone that has been reported to possess a higher inhibitory ability for tyrosinase compared to that of arbutin, but 10-fold lower than that of hydroquinone.⁸⁷ Arbutin and deoxyarbutin act by competitively inhibiting tyrosinase and 5,6-hydroxyindole-2-carboxylic acid polymerase. In addition, they disrupt melanosome maturation, but they are, overall, less cytotoxic than hydroquinone.⁸⁸

Very few randomized clinical trials have been conducted in order to assess the effectiveness of arbutin in the treatment of melasma. In a small trial that included 30 patients who were randomized to receive natural ellagic acid or synthetic ellagic acid or arbutin, it was reported that a statistically important difference between pre- and post-treatment levels of melanin was observed.⁸⁸ Similarly, in a recent single-arm study with 33 patients, a regimen containing nicotinamide 4%, arbutin 3%, bisabolol 1%, and retinaldehyde 0.05% was reported to be associated with statistically important melasma improvement as demonstrated by MASI scores (mean reduction in MASI score was $2.25 \pm 1.87/P < 0.0001$ in day 60).⁸⁹ Although arbutin has been associated with promising results in the treatment of melasma, more randomized clinical trials are needed. In general, it is used in concentrations of 3%, but caution is suggested since its use may cause paradoxical hyperpigmentation.³⁰

Other topical depigmenting agents

A number of depigmenting agents, both synthetic and natural occurring, have been investigated in the treatment of hyperpigmentation disorders. These compounds can be encountered in numerous prescription combination regimens as well as in many over-the-counter formulations. In addition, a number of clinical trials assessing the efficacy of new possible treatments are currently recruiting or ongoing. For instance, a trial comparing the efficacy of 4% HQ and 2% miconazole creams is currently recruiting patients (NCT01661556). However, many widely used depigmenting agents (in over-the-counter formulations) have never been tested in a clinical trial setting. The fact that so many topical regimens exist demonstrates an unmet need in the treatment of melasma. A summary of these agents can be found in Table 30.3.^{90–98} Other depigmenting agents include linoleic acid, orchid extracts, magnolignan, traxenamic acid, cinnamic acid, alphalipoic acid, thioctic acid, dihydrolipoic acid, flavonoids, gentisic acid, ellagic acid, aloesin, and so on.⁹⁰

Chemical peels

The chemical peels used for the treatment of hyperpigmentation disorders act by causing a controlled destruction of the superficial part of the epidermis and, therefore, removal of the unwanted excess pigment. This process is achieved by topical application of a specific chemical agent that leads to exfoliation of the skin followed by the regeneration of the epidermis.⁹⁹ In general, peels have been associated with acceptable results in the treatment of melasma, especially when used in conjunction with other types of topical treatments. It must be mentioned, however, that chemical peels should be used with extreme caution when treating darker skin phototypes, since post-inflammatory pigmentation is not uncommon in such patients.¹⁰⁰ The most commonly used peels include GA peels, salicylic acid (SA), mandelic SA, pyruvic acid, Jessner solution, and trichloroacetic acid (TCA), among others, but they often provide unsatisfactory results.¹⁰⁰

Alpha hydroxy peels

GA and lactic acid peels belong to the category of alpha hydroxy peels and are some of the most commonly used peels in the treatment of melasma. GA peels are thought to exert a pH-dependent inhibitory effect on tyrosinase activity.¹⁴ They are superficial to medium-depth peels depending on the concentration used, number of layers applied, and the duration of the application.¹⁰¹

Various studies have been conducted in the past assessing the efficacy of GA peels in the treatment of melasma, yielding conflicting data. In a study by Lin et al., GA peels in concentrations of 20%–70% were administered in 10 Asian females, either as monotherapy or as combination with 2% HQ and 10% GA peels. Overall, an improvement of melasma was reported; however, there was no statistically important difference noted between groups. In addition, a painful burn causing PIH was reported in the GA group.⁶⁸ Similarly, Hurley et al. reported that the combination of 20% GA peels and 4% HQ did not yield better results compared to 4% HQ monotherapy, although improvement from baseline MASI scores were observed in both groups.¹⁰² In a recent study by Faghihi et al., the safety and efficacy of 1% isotretinoin peel was compared to that of a 70% GA peel in 63 female melasma patients. After four treatment sessions, a similar improvement was observed in both treatment groups, with more adverse events reported in the GA treatment arm.¹⁰³ Similar results were reported in various other trials.^{100,104} Moderate results have also been reported in a study where the efficacy of a combination of GA 70% and TCA 35% was compared to cryotherapy in the treatment of solar lentigines. In this study, clearing was achieved in 17.4% and 21.7% of patients treated with the chemical peels and cryotherapy, respectively.¹⁰⁵ However, GA peels may be able to improve treatment results when used in combination with other treatment modalities. For instance, Erbil et al. reported that GA peels that are applied in combination with 20% AA and 0.1% adapalene are associated with

Table 30.3 Summary of other depigmenting agents.

Depigmenting agent	Source/ composition	Mode of action	Data on efficacy	Recommended dose	Adverse events
Licorice extract (glabridin, liquirtin, isoliquirtin)	Root of the perennial herb <i>Glycyrrhiza glabra</i>	Tyrosinase inhibition Possible anti-inflammatory action	Very limited data from clinical trials, possibly beneficial	Not specified	Mild irritation Erythema Mild burning sensation
Soy (genistein: soybean trypsin inhibitor/STI, diadzein: Bowman Birk Inhibitor [BBI])	Plant derivative	Inhibit melanosome transfer to keratinocytes (inhibit the protease-activated receptor-2 pathway) Possible antioxidant properties	Very limited data One RCT in 65 female patients by Wall et al.: possibly beneficial effect	Not specified	Well tolerated, limited data are available
Niacinamide	Vitamin B3	Reversibly inhibits the transfer of melanosomes from melanocytes to keratinocytes	Very limited data. One RCT by Navarette–Solis et al. in 27 patients, demonstrated acceptable efficacy of 4% formulation compared to 4% HQ cream	2% to 5% concentration formulations	Erythema Pruritus Burning
<i>N</i> -acetyl-glucosamine (NAG)	Amino sugar (precursor of hyaluronic acid)	Inhibits the glycosylation of tyrosinase	Very limited data. In one RCT by Bissett et al., a beneficial effect was reported. NAG has also been combined with niacinamide, providing beneficial results.	2% formulation	Mild-to-moderate skin irritation Well tolerated
<i>N</i> -acetyl-4- <i>S</i> -cysteaminyphenol (NCAP)	Phenolic compound	Alternative substrate for tyrosinase	Very limited data. One small study by Jimbow et al. reported moderate efficacy.	4% formulation	Mild-to-moderate skin irritation Well tolerated
Rucinol	Derivative of resorcinol/ phenolic compound	Inhibition of tyrosinase and TRP-1 (dose-dependent effect)	Very limited data. One study by Khemis et al. in 35 female patients reported beneficial effect. Another study assessing the efficacy of 4- <i>n</i> -butylresorcinol by Huh et al. also reported beneficial effect.	0.3% formulation: Rucinol 0.1% formulation: 4- <i>n</i> -butylresorcinol	Well tolerated
Dioic acid	Dicarboxylic acid group	Agonist to nuclear PPAR (regulates tyrosinase transcription/ melanosome transfer)	Limited data. In a study by Tirado-Sánchez et al. that included 96 patients, it was reported that dioic acid showed similar efficacy to 2% HQ.	1% formulation	Erythema Burning Pruritus Acneiform reaction

(Continued)

Table 30.3 (Continued) Summary of other depigmenting agents.

Depigmenting agent	Source/Composition	Mode of action	Data on efficacy	Recommended dose	Adverse events
Octadecenedioic acid (ODA)	Dicarboxylic acid group	Similar to that of dioic acid	Limited data. In one small study including 21 Chinese patients, it was reported that ODA showed acceptable efficacy compared to 2% arbutin	1% formulation	Well tolerated, limited data are available
Undecylenoyl phenylalanine (UP)		Acts as α -melanocyte-stimulating hormone (α -MSH) and beta-adrenergic receptor (β -ADR) antagonist	Limited data. A study by Katoulis et al. that included 37 patients with melasma reported beneficial results. Also, in a previous study by Bissett et al., it was reported that the combination of UP and niacinamide 5% was more effective than niacinamide 5% monotherapy.	2% formulation	Erythema Pruritus Burning sensation

Source: Draelos ZD, *Dermatol Ther*, 20(5):308–13, 2007; Bissett DL et al., *J Cosmet Dermatol*, 8(4):260–6, 2009; Katoulis A et al., *J Cosmet Dermatol*, 13(2):86–90, 2014; Sarkar R et al., *Indian J Dermatol Venereol Leprol*, 78(4):417–28, 2012; Amer M and Metwalli M, *Int J Dermatol*, 39(4):299–301, 2000; Alexis AF and Blackcloud P, *J Drugs Dermatol*, 12(9 Suppl):s123–7, 2013; Wallo W et al., *J Drugs Dermatol*, 6(9):917–22, 2007; Navarrete-Solis J et al., *Dermatol Res Pract*, 2011:379173, 2011; Bissett DL et al., *J Cosmet Dermatol*, 6(1):20–6, 2007; Jimbow K, *Arch Dermatol*, 127(10):1528–34, 1991; Khemis A et al., *Br J Dermatol*, 156(5):997–1004, 2007; Tirado-Sanchez A et al., *Int J Dermatol*, 48(8):893–5, 2009.

better results compared to topical therapy only. However it is indicated that GA concentrations >50% are required for this result.¹⁰⁶ Similarly, in a study by Rendon et al., where a triple-combination cream was used alternating with a series of GA peels, it was demonstrated that up to 90% of patients had responded to treatment and 63% had achieved clear or almost clear skin after 12 weeks of treatment.¹⁰⁷

GA peels are generally safe and are associated with only mild adverse events. These include erythema and mild exfoliation. It is important to advise patients to avoid sun exposure after the treatment session and to use sunscreens and moisturizers at night. An important adverse event that may be of concern, especially in darker phototypes, is PIH. For this reason, high-concentration GA peels (>50%) should be avoided in dark-skinned patients.

Beta hydroxy peels

SA peels belong to the category of beta hydroxy peels. SA is an anti-inflammatory agent and has been shown to possess a depigmenting potential in a small number of trials. In a study by Ejaz et al. where the efficacy of Jessner's peel (14% SA, 14% lactic acid, and 14% resorcinol in alcohol) was compared to that of a 30% SA peel, a significant reduction in MASI scores was reported in both groups, but no difference was noted between the two regimens.¹⁰⁸ Interestingly, in a study by Kodali et al., the combination of 20%–30%

SA peel with 4% HQ did not provide a superior therapeutic outcome compared to HQ monotherapy.¹⁰⁹ Similar results are reported in various other trials.^{100,110} SA peels may be beneficial, however, in patients with PIH attributed to acne. For instance, in a study by Ahn et al. where colorimetric methods were used to assess the efficacy of 30% SA peels, applied biweekly for 3 months, a mild improvement of PIH was observed.¹¹¹ Similar results were demonstrated in other studies as well.¹¹² Although the improvement observed in PIH, after application of SA peels, did not reach statistical significance, they may present an alternative (or adjuvant) in the management of patients with acne, and especially for those who present with darker phototypes.

Overall, the adverse effects associated with the use of SA peels are generally mild, including crusting, transient hyperpigmentation and hypopigmentation, and temporary dryness.

CONCLUSIONS

Acquired hyperpigmentation disorders are relatively common disorders, associated with significant psychological morbidity for patients, as they represent a visible aesthetic problem. At the same time, they are also a source of concern for treating dermatologists as few treatments are adequately effective. Melasma, solar lentigines, and PIH are only a few of the hyperpigmentation disorders

encountered in the dermatological everyday practice. Regardless of the etiology of the hyperpigmentations, patients should always be informed about the importance of sun protection and the fact that no treatment provides permanent results. Topical depigmenting agents, used alone or in combination with chemical peels, can produce acceptable results in the treatment of hyperpigmentations; however, it is important for patients to realize that all currently available treatment regimens need sufficient time to yield results and must be combined with highly effective sun protective measures in order to prevent disease recurrence.

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Chemical peels

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INTRODUCTION

Hyperpigmentation is one of the most common cosmetic causes for consultation in dermatology for all skin types but especially for those with dark skin or mixture of ethnicities. It is the result of an increase in cutaneous melanin deposition either by increased melanin synthesis or, less commonly, by a greater number of melanocytes.¹ Whether the melanin is deposited in the epidermis or dermis is important therapeutically because dermal hyperpigmentation is much more challenging to treat.²

Melasma and post-inflammatory hyperpigmentation (PIH) account for the majority of cases and are characterized by pigmented macules and patches distributed symmetrically in sun-exposed areas of the forehead, cheeks, and chin in melasma, and irregularly in areas of inflammation or an inciting traumatic event in the case of PIH.¹ Other pigmented lesions that lead patients to consult for esthetic reasons are attributed to photoaging of the skin because of chronic exposure to ultraviolet (UV) radiation such as solar lentigos, lentigines, and pigmented actinic keratoses.

Chemical peels are a widely used, fast, safe, and effective office-based treatment that may be used for various cosmetic indications, such as fine lines and photoaging, but also as primary or adjunct therapies for acne, scarring, and pigmentary disorders.³ They have been utilized in the treatment of pigment dyschromias as an additional useful tool that can be used by itself or in combination with other treatments to combat hyperpigmentation.

However, the use of chemical peels is not a first-line treatment for melasma as the published evidence is only fair or poor (Quality of evidence B or C).¹ This chapter presents different existing peels and their possible uses in hyperpigmentation as well as peels used for the treatment of photoaging.

DEFINITION AND CLASSIFICATION OF CHEMICAL PEELS

Chemical peeling is performed by the application of one or more exfoliating agents to the skin to produce controlled partial-thickness ablation, creating in essence a type of controlled wound.

Chemical peels remove the outer skin layers through either keratolysis or keratocoagulation.

- Keratolytic agents (alpha hydroxy acids) penetrate through the stratum corneum and disrupt corneocyte adhesion by breaking intercellular desmosomal bonds.
- Keratocoagulants (trichloroacetic acid [TCA]) destroy surface cells through protein denaturation and keratinocyte coagulation.

The effect with either mechanism is desquamation and acceleration of the epidermal renewal process.

Chemical peels are classified into three categories based on the *depth* of destruction caused by the treatment.⁴ Superficial peels penetrate the epidermis only, medium-depth peels damage the entire epidermis and papillary dermis, and deep peels create a wound to the level of the midreticular dermis.

Superficial peels result in a regular epidermal structure with uniform distribution of melanin and the elimination of melanin accumulations.^{3,5} Clinically, superficial peels impart a radiant complexion, treat melasma at the dermal-epidermal junction, and improve lentigines.^{4,6} Medium-depth or deep peels are also effective on lentigines and improve the complexion.^{4,6} They are contraindicated for melasma as they may cause PIH that aggravates the initial symptomatology. Precautions associated with their use should be proportional to the darkness of the skin to be treated.³

The depth of the peel depends on various parameters (Table 31.1) and is correlated with clinical changes, with the greatest change achieved by deep peels. However, the depth is also associated with longer healing times and the potential for complications.⁷ Superficial peels are very safe and tolerated with minimal to mild discomfort, such as transient burning, irritation, and erythema.^{7,8} Scarring is rare in superficial peels, as are PIH and infection. In medium and deep peels, lines of demarcation that are technique related can occur. This effect may be avoided by feathering the peel solution at junctions with nonpeeled skin. Side effects of deeper peels may also include pigmentary changes (e.g., PIH for dark-skinned individuals), infections, allergic reactions, improper healing, hypersensitivity, disease exacerbation, and those caused by improper application of the agent.^{4,9}

For all peels, care must be taken to prophylactically treat patients with a history of herpes simplex infections. Herpetic episodes, usually on the lip or above the vermillion border, may be prevented with prophylactic oral acyclovir, valacyclovir hydrochloride, or famciclovir.^{10,11} Antiviral agents are especially useful in patients who indicate a strong history of multiple herpetic lesions each year.

PEELING PROCEDURE

The process and the technique of a peeling procedure are largely determined by the chemical's nature and the concentration of the applied peeling substance. However, most peeling procedures follow a typical sequence of steps³:

1. Pre-peeling preparation (priming)
2. Pretreatment cleansing
3. Treatment
4. Post-peeling care

Table 31.1 Variables determining the depth of a peel.

- Type of the peeling agent
- pH of the peeling agent
- Concentration of the peeling agent
- Time of application
- Layers of the agent applied
- Application technique
- Prepping of the skin
- Patient skin type

The priming phase and the post-peeling care are very important when the peel is destined to treat hyperpigmentation as they are essential to treatment success. In order to avoid PIH, the epidermal melanogenesis needs to be inactivated^{4,12} by the daily use of sunscreens. In patients with a dark phototype, an additional treatment with a priming agent may be required.³ Apart from decreasing PIH, preparing the skin is a useful adjunctive measure that boosts the effect of the peel. Priming ensures uniform penetration of the peeling agent, enhances healing, and maintains the results achieved with the chemical peel.¹³ It involves the application of a topical depigmenting agent like hydroquinone, tretinoin, or glycolic acid (GA) 2 weeks before the planned day of peel.¹³ Studies have been conducted to assess the benefit of priming agents as adjuncts to chemical peels and have demonstrated that hydroquinone 2% gives better clinical results compared with 0.025% tretinoin when used as an adjunct with either GA peels or 10%–30% TCA peels.^{13–15}

The most important post-peel measurement once the skin is re-epithelialized is use of UV protection and visible light protection by lifelong application of an appropriate sunscreen.

PEELING AGENTS

Alpha-hydroxy acid/GA peels

Alpha-hydroxy acids (AHAs) have become popularized as “fruit acids” and that name has had a great influence on the interest shown by patients.¹⁶ They are long-established peels that have practically no downtime (lunchtime peels) and are usually superficial depth peels. They have therapeutic as well as cosmetic benefits when used on skin.¹⁷

Glycolic acid (hydroxyethanoic acid, hydroxyacetic acid) (GA) is the smallest AHA, with just two carbon atoms. It was originally extracted from sugarcane, but the acid used in treatment today is synthesized chemically. It penetrates the skin, easily making it a widely used peeling agent.¹⁸

GA and AHA peels produce the best results if they are preceded by careful preparation and followed by long-term daily cosmetic care. The products usually utilized to prepare the skin are sunscreens, retinoids, AHA, and tyrosinase inhibitors (hydroquinone, kojic acid, azelaic acid, arbutin, etc). It is important to stop priming agents around 1 week before the peel.¹⁸ Epidermolysis may occur if the patient has used topical retinoids, anti-acne creams, or skin lighteners in days before the peel.

The procedure of application is quite straightforward. After the skin has been cleansed and degreased, GA solution is applied using cotton buds or a brush in a sequential manner starting from the forehead to the left cheek, the chin, to the right cheek to cover the entire face.¹⁸ Care is taken to protect the eyes and the corners of the nose and lips. The peel is neutralized within 3–5 minutes, or when uniform erythema is seen. If frosting is observed in any particular area before the set time or end point, it is important to neutralize the peel immediately as it signifies epidermolysis.¹⁸

GA peels are commercially available as free acids, partially neutralized (higher pH), buffered, or esterified solutions.¹⁹ GA is applied in solutions at concentrations varying between 25% and 70% and at a pH between 1 and 3; tolerance is generally good. The higher the concentration and the lower the pH, the deeper the peeling, but it stays relatively superficial. Epidermal regeneration should be expected within 3 to 5 days, and desquamation is usually well accepted.

GA is always used over several sessions (generally six) several weeks apart. As sessions progress, the concentration of the solution used and application time are progressively increased, depending on tolerance and the result obtained after preceding sessions. There should be a minimum interval of 2 weeks between two treatment sessions. Peel neutralization is extremely important, and it depends on erythema seen. However, in dark skin, it may be difficult to appreciate erythema.¹⁸ In such cases, it is better to time the peel between 3 and 5 minutes and judge the desired end point depending on the time.¹⁸

Repeated superficial peels with GA can gradually produce significant benefits in patients with melasma.^{20,21} GA at high concentrations (50%–70%) diminishes corneocyte adhesion in the upper layers of the epidermis, and indeed its epidermolytic effects have been largely used to treat cutaneous hyperpigmentations.^{22–24} In fact, GA may remove excessive epidermal pigmentation and increase the growth of normal undamaged cells underneath the lesions.²⁴

GA peels need to be properly neutralized to stop acidification of the skin.¹⁶ Applying acid to the skin saturates the ability of cells to resist acidification; excess acid must be neutralized to avoid burning. AHA peels can be neutralized with water or with basic solutions, such as ammonium salts, sodium bicarbonate, or sodium hydroxide.^{16,18}

Lactic acid (2-hydroxypropanoic acid) is the next shortest AHA after GA. Lactic acid occurs naturally in sour milk. After penetrating the skin, lactic acid is converted automatically and reversibly into pyruvic acid, the alpha-keto acid derivative of lactic acid. At identical concentrations, lactic acid destroys the epidermis more slowly than GA. Concentrations of lactic acid of 10%–20% or stronger begin to destroy the stratum corneum and stimulate skin regeneration. Lactic acid is also a better hydrator than urea or glycerol.¹⁶ Lactic acid has surprisingly not been used extensively as a peeling agent in the treatment of melasma, although it is a non-costly and readily available agent.¹³

The first pilot study on lactic acid was done by Sharquie et al.²⁵ who found it to be a safe and effective peeling agent for melasma in dark skin. In their study of 20 patients, 92% pure lactic acid was applied for a maximum of six sessions, and a significant fall in MASI (56%) was observed in all of the 12 patients who completed the study. Further, lactic acid was compared with a well-established peeling agent, Jessner's solution in a split-face design, and similar improvement was seen on both the sides with no relapse at a follow-up after 6 months.²⁶ These studies justify further experimentation with lactic acid as a peeling agent for dark skin.

Ascorbic acid or vitamin C is an AHA derivative. It has been shown to stimulate collagen production and reduce melanin production.¹⁶ Therefore, pretreatment, posttreatment, or parallel with the peels use of topicals containing vitamin C seems to be an interesting approach to boost the lightening effects.

Mandelic acid (MA) is one of the largest alpha hydroxy acids that penetrate the epidermis slowly and uniformly, making it an ideal peeling agent for sensitive skins.²⁷ MA peels are obtained from bitter almonds and have a low molecular weight. They exist in strength of 20%–50% and are often utilized for post-acne pigmentation because of their tolerability on dark skin.²⁸ Active acne lesions and hyperpigmented marks improve with MA peels owing to the antibacterial and anti-inflammatory properties. MA (20%, 30%, and 45%) shows synergistic results when used in combination with salicylic acid (SA) and retinoic acid peels and hence is incorporated in many peel formulations in various strengths.²⁸ The safety profile of this peel is high owing to the absence of post-peel irritation for Asian skin types.²⁹

Beta-hydroxy acids

Salicylic acid (SA) is a non-caustic, keratolytic, anti-inflammatory, lipophilic, sebolytic peel that causes epidermal exfoliation^{28,30} and is quite useful in treating acne. SA peels have also been used for the treatment of melasma and post-inflammatory pigmentation in acne. SA has been used for a long time, but is used much less frequently since the popularity of peels with AHA. This superficial peel is employed at weekly sessions for 6–8 weeks. The most common concentration used is 20%–30%. For these peels, the end point is the pseudofrost formed when the SA crystallizes. This type of agent is very safe, and patients generally tolerate the procedure well. Grimes³¹ studied 20%–30% SA peels in skin of color and reported marked clearance in PIH in all patients. There was a rapid resolution of papules, pustules, and comedones in acne patients. Moderate to significant improvement occurred in 89% of acne patients and 100% of PIH patients. Some patients had mild dryness and crusting with transient hyperpigmentation.

SA is also used in combination peels, with the most famous one being *Jessner's peel* (14% SA, 14% lactic acid, and 14% resorcinol in alcohol). In a study conducted by Ejaz et al.³² comparing Jessner's peel with a 30% plain SA peel, there was no significant difference in MASI scores at

12 or 24 weeks between the two regimens, with significant reductions in MASI scores from baseline in both groups. There was also excessive crusting of the face noted in both groups.

Another study comparing three interventions—Jessner's peel versus TCA 20% peel versus topical hydroquinone 2% and kojic acid for 16 weeks—found that the MASI score for TCA 20% showed a greater reduction than Jessner's peel or topical hydroquinone 2% with kojic acid at the 16-week follow-up visit.³³ However, PIH was more common in the chemical peel groups, with the TCA peel group having a higher rate than the Jessner's peel group.

A peel using a lipophilic derivative of SA, *lipo-hydroxy acid* (LHA), has recently been introduced.^{3,12} It is the newest product in this category. The LHA is used in 5% and 10% concentrations.

TCA peels

TCA is used for its peeling properties and determines a progressive exfoliation of the skin and the removal of the pigment from the upper layers of the epidermis.³⁴ Its biological mechanism of action is related to a coagulative necrosis of the superficial proteins of epithelial cutaneous cells, followed by cellular death. The use of TCA produces an evident exfoliation of the skin, followed by the appearance of crusted lesions that may persist for a few days to 2–3 weeks. For this reason, this type of peel is not as well accepted by some patients as softer peels. However, its great advantage is the lower number of treatments required for good cosmetic results.²³

Classic TCA peels in a simple aqueous solution always require around 1 month's intensive pre-peel preparation. This preparation stimulates keratinocyte regeneration and reduces the risk of post-inflammatory pigmentary changes and scarring. The products usually used to prepare the skin are sunscreens, tretinoin, AHAs, and tyrosinase inhibitors (hydroquinone, kojic acid, azelaic acid, arbutin, etc).

The degree of penetration depends on the peel's concentration: a 15%–25% TCA solution causes a coagulative necrosis confined to the epidermis and therefore acts as a superficial peel, whereas a 30%–40% TCA solution causes a necrosis of the superficial and the middle dermis and provides a medium peel. Higher TCA concentrations (>40%) determine a necrosis of the whole dermis and are used as medium/deep peels.^{35,36} The depth reached is reflected by symptomatology and requires considerable experience to perform precisely. A TCA peel is thus highly operator dependent. The physician should achieve a level II to level III frosting. The white frosting indicates kerato-coagulation or protein denaturation of keratin and at that point the reaction is complete. Level I frosting is erythema with a stringy or blotchy frosting, seen with light chemical peels. Level II frosting is defined as white-coated frosting with erythema showing through. A level III frosting, which is associated with penetration through the papillary dermis, is a solid white enamel frosting with little or no background of erythema.³⁷ Adverse events such as scars and hyperpigmented or hypopigmented lesions might

occur with the use of >30% TCA.^{35,37} These concentrations should be avoided in the treatment of hyperpigmented lesions where the use of 15%–25% solutions is preferred. However, the dermal component of melasma is resistant to low TCA concentrations. In these cases, treatment sessions should start with low concentrations in order to eliminate the epidermal component, and if there is a dermal component remaining, it can be addressed by a more circumscribed use of a higher TCA concentration. Cotellessa et al.²³ demonstrated that peels with 15%–25% TCA obtained complete regression of cutaneous lesions in 40% of cases and a significant lightening in 50% of cases after three to eight applications.

Combinations of products with a 35% TCA formula have been found equally effective in producing controlled damage equivalent to that of a 50% TCA without the risk of side effects³⁷ (Figure 31.1). Brody first developed the use of solid CO₂ applied with acetone to the skin as a freezing technique before the application of 35% TCA.³⁸ The preliminary freezing appears to break the epidermal barrier for a more even and complete penetration of the 35% TCA.³⁸



(a)



(b)

Figure 31.1 Patient treated with Monheit's procedure: Jessner's peel followed by TCA 35%. (a) Before treatment, (b) after treatment. (Courtesy of Dr. Yannis Neofytou.)

Monheit then demonstrated the use of Jessner's solution before the application of 35% TCA. Jessner's solution was found effective in destroying the epidermal barrier by breaking up individual epidermal cells. This also allows a deeper penetration of the 35% TCA and a more even application of the peeling solution.³⁹ Similarly, Coleman has demonstrated the use of 70% GA before the application of 35% TCA. Its effect has been very similar to that of Jessner's solution.⁴⁰ All three combinations have proven to be as effective as the use of 50% TCA with a greater safety margin.³⁷ The application of acid and resultant frosting is better controlled with the combination so that the "hot spots" with higher concentrations of TCA can be controlled, creating an even peel with less incidence of dyschromias and scarring.

Medium-depth peels are effective on lentigines and improve the complexion. However, they are contraindicated for melasma as they may cause PIH that aggravates the initial symptomatology. Precautions associated with their use are proportional to the darkness of the skin to be treated.

PIH and berloque dermatitis usually respond well to TCA; they can be treated in the same way as melasma, but have a better prognosis as the original cause disappears after treatment, unlike melasma, which often persists or recurs.¹⁶

Recently, focal chemical peels with TCA have been introduced for the treatment of pigmentary disorders to minimize the side effects such as pain or scarring associated with medium-to-deep chemical peeling.⁴¹ The focal use of TCA 30%–50% is quite well tolerated in dark-skinned patients with less side effects for the lower concentrations. Benign pigmented lesions, including seborrheic keratosis (Figure 31.2), solar lentigines, melasma, and freckles, are focally distributed. In order to maximize the effects of TCA and to overcome complications such as



Figure 31.2 Dark-skinned patient treated with focal application of 30% TCA for multiple pigmented seborrheic keratosis. (Courtesy of Dr. Myrto Trakatelli.)

scarring, hyperpigmentation, and hypopigmentation, a circumscribed application technique was proposed consisting of the focal application of higher TCA concentrations on the pigmented areas only by using a sharpened wooden applicator.⁴² This technique appeared as a safe and effective modality for the treatment of benign pigmented lesions with no significant complications. In a controlled, prospective study to compare the efficacy of a focal medium-depth chemical peel regimen using 70% GA and 35% TCA with cryosurgery in the treatment of solar lentigines of the hands, no statistically significant improvement was found between the two methods. The authors however suggested that treatment of the solar lentigines with a focal medium-depth chemical peel may be clinically superior to treatment with cryosurgery, owing to the paucity of side effects, such as hypopigmentation and pain, associated with the chemical peel regimen.

Phenol peels/peels for photoaging

The standard-depth deep chemical resurfacing procedure is a phenol peel. Phenol peels may be performed with various formulations, such as pure phenol (which is really 88%) or phenol mixed with soap, water, croton oil, and sometimes olive oil. These formulas have such names as Baker-Gordon, Venner-Kellson, Maschek-Truppmann, and Grade.

After a phenol peel, melanocytes can no longer produce melanin. Thus, it provides a definite and effective treatment in one single session. This treatment is ruled out as extreme for melasma alone.¹⁶

The structural and functional deterioration of skin caused by chronic UV light exposure is named photodamage. It includes the following symptoms: pigmentation alterations (dyschromia, solar lentigos), wrinkles, spider veins, elastin changes that manifest as both laxity and leathery skin, pre-malignant lesions (actinic keratosis [AK]), and malignant lesions. A wide range of chemical peels have been used to treat photodamaged skin: tretinoin,⁴³ hydroxyl acids,⁴⁴ and fluorouracil.^{45–48}

Medium to deep peelings may be used in the treatment of photodamaged skin. Textural changes, dyschromia,

solar lentigos, wrinkles, and thin AK can be improved by using peels capable of denaturalizing surface keratin and other proteins of dermis and outer dermis⁴⁹ (papillary and reticular dermis⁵⁰), maximizing new collagen regeneration. Peels can be combined with procedures to further enhance results.^{51–54}

Deep peelings are usually performed with phenol-based solutions such as Baker/Gordon phenol peel (Phenol 88%, croton oil 3 drops, distilled water 2 cc, Septisol liquid soap 8 drops) or Hetter phenol-croton peel.⁵⁵ In the latter, depth of the peel seems to be more dependent on the concentration of croton oil than phenol. Hetter formulas use croton oil into 50% phenol, causing a marked increase in the depth of peeling into the dermis⁵⁶ while reducing the risk of cardiac toxicity. Regardless of the concentration used, the number of coats applied has an additive effect: even a weak concentration can lead to deep involvement⁵⁷ (Table 31.2). Clinical improvement of photodamaged skin can be evaluated as a reduction in pigmented lesions and dyschromia and number of AK as well as texture changes (Figures 31.2 and 31.3). Bagatin et al.⁴⁶ reported up to 80% AK clearance using a combination of Jessner's solution or 70% GA with 5% 5-fluorouracil solution in 8-week pulses. Kaminaka et al.⁵⁸ have reported up to 84.8% complete response after one to eight phenol peel sessions for treating AK and Bowen disease. This group has also demonstrated the efficacy in nevoid basal cell carcinoma.⁵⁹ Dainichi et al.⁶⁰ have reported that chemical peeling with SA in polyethylene glycol vehicle (SA-PEG) suppresses skin tumor development in UVB-irradiated hairless mice by suppressing the proliferation of p53-positive cells in the skin. P53 mutations are a crucial event in UV-induced multistep carcinogenesis.⁶¹ In an experimental model, chemical peeling (GA, SA, and TCA) can further prevent tumor formation by removing photodamaged cells.⁶²

CONCLUSIONS

Despite their wide usage in dermatological and aesthetic practice, scientific evidence points out that chemical

Table 31.2 Hetter peel formulas with a 35% phenol vehicle.

	Croton oil				
	0.2%	0.4%	0.8%	1.2%	1.6%
Water	5.5 mL	5.5 mL	5.5 mL	5.5 mL	5.5 mL
Septisol	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL
USP phenol 88%	3.5 mL	3.0 mL	2.0 mL	1.0 mL	0.0 mL
Stock solution	0.5 mL	1.0 mL	2.0 mL	3.0 mL	4.0 mL
containing Phenol and croton oil (see below)					
Total	10 mL	10 mL	10 mL	10 mL	10 mL

Source: Bensimon RH. Croton oil peels. *Aesthet Surg J*, 2008 Jan–Feb;28(1):33–45 (with permission).

Note: 0.1% = 1 mL of 0.4% + 1.2 mL Phenol + 1.8 mL water; 0.05% = 1 mL of 0.2% + 1.2 mL Phenol + 1.8 mL water; Stock solution = 24 mL phenol + 1 mL croton oil (0.04 mL croton oil) or 4% croton oil (1 mL stock solution).



Figure 31.3 (a) Patient treated with two sessions 1 month apart of Nomelan peeling by Sesderma (20% phenol, TCA, SA, GA, and retinol). (Images taken with Vectra H1 by Canfield.) (b) Same images analyzed with RBX technology (Canfield) for unequaled visualization of red skin components for unequaled visualization and monitoring improvement of photodamage skin conditions. (Courtesy of Dr. Paola Pasquali.)

peels at best remain second-line or adjunct treatment for melasma with or without combination with skin-lightening agents. First-line therapy usually consists of topical compounds that affect the melanin synthesis pathway, broad-spectrum photoprotection, and camouflage. It is recommended that photoprotection and modified Kligman's formula should be used as a first-line therapy for up to 12 weeks.⁶³ In most patients, maintenance therapy will be necessary with non-hydroquinone products or fixed triple combination intermittently, twice a week, or less often. Concomitant camouflage should be offered to the patient at any stage during therapy. Monthly follow-ups are recommended to assess the compliance, tolerance, and efficacy of therapy.

Chemical peels are often added in second-line therapy. There is a medium-quality evidence to suggest that undergoing serial chemical peels with GA, SA, or TCA is moderately effective in the treatment of melasma.⁶³ GA peels are used as an adjunctive therapy in refractory cases of epidermal melasma as they enhance the efficacy of topical regimen.

Clinicians should remember that there can be excellent synergy between peels and other procedures.⁷ Chemical peels are most effectively used in combination with a topical, at-home regimen, which, depending on the condition, may include exfoliating or moisturizing products, bleaching agents, or retinoids. Using peels less frequently but on a continuing basis is beneficial to help keep improvement ongoing, especially for superficial peels.⁷

Table 31.3 Practical tips for counseling of patients before chemical peels.

- Evaluation of *psychological aspects*—judge motivation and expectations of patient
- Explanation on *realistic expectations* (media-hyped patient = unrealistic expectations)
- Explanation on nature of treatment, expected outcome—always downplay *degree of improvement expected*
- Information on *time for recovery* of normal skin and importance of *maintenance regimens and lifetime photoprotection*
- Discussion of *side effects*, likely and unlikely complications, particularly pigmentation changes

The choice of peeling agent, the peel concentration, and the frequency and duration of peels are all important to achieve satisfactory results. Special attention is required to three key points as they optimize the treatment: use of priming agents, advice regarding photoprotection, and need for maintenance peels. Finally, the most important step for a successful chemical peel program is patient selection. Patients who are willing to undergo continued treatment are likely to be the best candidates. Counseling of patients (Table 31.3) considered for chemical peel treatment is a critical element to a successful final outcome both on the level of skin dyschromia improvement and on the very important level of patient satisfaction.

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Cryotherapy

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INTRODUCTION

Cryotherapy, or better said, cryosurgery is the destruction of tissue using subzero temperatures. It stands as one of the most commonly used surgical techniques among dermatologists and family physicians, as it is relatively simple to perform, versatile, and inexpensive when compared to other surgical alternatives.¹ It is a surgical option for treating benign nonmelanocytic skin lesions such as lentigo solaris, ephelides, and seborrheic keratosis (SK), and premalignant and malignant nonmelanocytic skin lesions such as pigmented actinic keratosis and pigmented basal cell carcinomas (BCCs).

As melanocytes are extremely sensitive to subzero temperatures, deep freezing tends to leave hypopigmented areas. In skin phototypes III or higher, even superficial freezing could result in hypo/hyperpigmentation, making it mandatory to perform a small trial treatment in the less visible area before proceeding to treat a large number of lesions.

PRINCIPLES OF CRYOBIOLOGY

Cryosurgery uses extremely low temperatures to induce irreversible damage to tissues. There is direct injury as a result of extra- and intracellular ice crystal formation. These crystals provoke cell lysis, a damage that occurs during the freezing phase and in the center of the treated lesion.

The indirect injury relates to vascular damage: stasis, ischemia, endothelial damage, and necrosis. This starts during thawing and at the periphery of the lesion.

Later events are apoptosis, at the periphery of the cryoinjury. It starts up to 8 hours after rewarming.

Immune-related events (T-cell response mediated by dendritic cells) are part of a late-occurring process and occur at a distance from the freezing site (Table 32.1).²

For these events to occur, freezing has to be fast and thawing slow. Rapid heat transfer is possible when there is a large temperature gap between the cryogen and the tissue.

Healing occurs by second intention, and cryosurgery seems to be an angiogenic stimulator that promotes such healing.³

Cold spreads in isotherms. The lowest temperature and destruction will be at the center of the cryolesion; the highest temperature will be at the periphery. By applying these concepts, one can infer that the temperature measured at the periphery of the lesion—using noninvasive infrared technology—will allow knowing the temperature at the bottom of the lesion.

CRYOGEN SELECTION

Cryogens are the substances used to produce low temperatures, and cryogenic liquids are liquefied gases that are kept in their liquid state at very low temperatures.⁴ They turn into gases at room temperatures. The ideal cryogen is the one that boils at very low temperatures, needs to be safe when being handled (gases used in medicine are classified under inert gases as they do not react chemically nor are flammable), and is easily obtainable.

The most commonly used cryogen is liquid nitrogen (LN) whose boiling point is -195.8°C . It is ideal for both benign and malignant lesions. Other commonly used cryogens are shown in Table 32.2.⁵

EQUIPMENT⁶

Dewars

LN needs to be stored in special containers constructed with insulating materials to maintain the cryogen for the longest possible time. They are kept closed with special loose-fitting lids that maintain the cryogen from evaporating while allowing excess pressure to vent; lids also prevent entrance of air or moisture.

They come in different sizes: 4, 5, 10, 20, 30, and 50 L. The smaller the dewar, the less it will cost to refill but the less time it will last. Larger dewars preserve LN for longer periods of time (10 L has a static preservation of 6–8 weeks; 20 L, 8–12 weeks; 30 L, 16 weeks).

LN can be withdrawn by using either a permanent device—that is, affixed to the top of the thermos and has faucet-like on/off control—or a removable one (needs to be removed after each usage) that offers instant pressure for withdrawal.

Cryosurgical units

Cryosurgical units are a fundamental part of cryosurgical equipment. They deliver vaporized gas in a standardized manner making cotton swabs obsolete. These units deliver cryogens through different size tips (openings) or probes in a safe, precise, and controlled manner.

For LN, they are available in 300, 350, and 500 cc bottles, which is more than sufficient for a routine day work and can be safely refilled as many times as needed.

Attachments for cryosurgical units

Spraying tips or apertures are by far the most commonly used attachments. They are adjuncts screwed at the release ending and come in different diameters (0.33 up to 1 mm, named A to D or 1 to 4 depending on the manufacturer). There are rigid and bendable extensions as well as adapters

Table 32.1 Molecular basis of cryosurgical cell destruction.

Mechanism		Time of cycle	Location
Direct injury	Extra- and intracellular ice crystal formation Necrosis	Freezing phase	Center of lesion
Vascular injury	Stasis Endothelial damage Microcirculatory failure Necrosis	Thawing phase	Periphery of the lesion
Apoptosis	Cell death by apoptosis	Up to 8 hours after rewarming	Periphery of the lesion
Immune response	T-cell response mediated by dendritic cells	Late event	Whole body

Source: With kind permission from Springer Science+Business Media: *Cryosurgery: A Practical Manual*, 1st ed. Pasquali P, ed., Kisis J, Zavorins A. Cryobiology and thermodynamics, Chapter 2, 2015, pp. 19–32.

Table 32.2 Temperature of some commonly used cryogens.

Temperature of common cryogens	
LN	−195.8°C
Argon gas	−185.8°C
Nitrous oxide (N ₂ O)	−88.48°C
Carbon dioxide (CO ₂)	−78.5°C
Other compressed gases	−55°C to −75°C

available to increase precision and to reach areas (like the back of the mouth or ear canal). The so-called acne aperture (Brymill®) is the option ideal for peelings. Luer-lock adapters allow using needles with different gauge extending the diameter options.

Lexan plates, rubber cones, and otoscope specula tips can be used to restrain sprayed LN. They are made of nonconducting materials.

Probes are metal-built close LN circuits that can be screwed at the releasing end of the unit. They come in different shapes to adjust to the lesion and are meant to contact the surface. Most are Teflon-coated to avoid sticking to the lesion surface. Previous freezing before attachment will further reduce sticking.

Other equipment

Tweezers can be used to grasp exophytic lesions. They need to be partially immersed in LN and left immersed until it stops boiling. They are commercially available (Teflon coated).

CRYOSURGICAL TECHNIQUES

There are six techniques that can be used:

1. Open technique or cryospray
2. Semi-open technique
3. Close or probe technique
4. Tweezer
5. Semiclosed or chamber technique
6. Intralesional technique

The first four can be used for the treatment of most common hyperpigmented lesions. The last two will not be discussed since they are reserved for other conditions (semi-closed is used whenever deep and potent freezing is required; intralesional is used in keloids and some palliative treatments).

Open technique or cryospray is the most popular technique. The aperture will be selected according to need: for delicate, superficial, and precise freezing, choose smaller apertures; for large lesions and faster freezing, choose larger apertures.

It is important to standardize the procedure maintaining the same distance and avoiding tilting the unit. Large apertures can spatter LN after some time and generate uncomfortable stinging sensation. Further precision can be obtained by releasing LN intermittently.

It is the ideal technique in patients with blood-born conditions, where skin contact or blood exposure techniques want to be avoided.

Semi-open technique: The use of rubber cones, lexan plates, or disposable otoscope tips will restrain sprayed LN and allow for a more precise, better localized, faster, and less painful procedure. By concentrating cryogen in one spot, freezing is faster and the reduction in pain could be explained by splattering avoidance. The opening needs to adjust to the lesion: if too small, the lesion will go undertreated; if too large, healthy skin will be treated unnecessarily.

Close or probe technique: Metal probes are ideal for treatments where temperature control, extreme cold temperatures required for cell destruction (cryosurgical treatment of malignant nodular tumors), deep and fast freezing, and/or pressure is required to reduce blood content (hemangioma's treatment). Small point probes are very useful for the treatment of sebaceous hyperplasia and rubi nevi.

Tweezers work well in small protruding lesions like skin tags. By allowing the freezing front to advance just to the base of the lesion, unnecessary post inflammatory pigmentation is avoided as healthy skin is spared. They are also very useful for cryobiopsy^{7,8} as well as treatments of protruding lesions in genitalia, oral cavity, or eyelids.

Preoperative Care

The majority of cryosurgical procedures need just minimal preparation. The first and most important condition before treatment is to be certain of the diagnosis. If in doubt, a previous biopsy is mandatory. Never freeze a lesion, particularly a pigmented one, if you are not certain of its nature.

Some important considerations are as follows:

Lesion selection. Certain conditions are ideal for cryosurgery (lentigo simplex, SK); others can be treated although not as first option treatment (dermatofibromas); and other are contraindicated (melasma).

Skin type. Types I and II tend to respond very well to cryosurgery; darker skin types could either hypopigment or hyperpigment even with superficial freezings; in general, the deeper the freezing, the larger the possibility to destroy melanocytes and therefore the greater chance of hypopigmentation.

Anatomical location. Face tends to respond very well and heals faster than legs. The farther from face, the longer expected healing time. It is important to let patients know the expected healing time.

Number of lesions. Freezing of benign lesions like lentigos or SK can be done without previous local anesthesia. Cryosurgery has the advantage of allowing multiple lesion treatment in one session.

Keratin is a poor conducting material. Reducing it can enhance cold penetration. This is the reason why it is best to shave warts before freezing or—for lentigos and actinic damage—prepare the skin a few weeks ahead with exfoliating creams such as salicylic acid ointments or retinoic acid creams. For cutaneous horns, cryoshaving the lesion leaves a sample for anatomopathological study and leaves a denudated area that can be easily treated with a probe (Figure 32.1).

COMMON HYPERPIGMENTED SKIN CONDITIONS AMENABLE TO CRYOSURGICAL TREATMENT

Table 32.3 shows the most common benign, premalignant, and malignant skin conditions amenable to cryosurgery.

Benign

For benign lesions, the best treatment is the one that only needs to be done once and leaves a cosmetically desirable result. It is in any case better to undertreat than over treat.

Table 32.3 Pigmented lesions amenable for cryosurgical treatment.

Type of lesion	Technique
Benign	
SK	Open, semi-open
Lentigo simplex, ephelides	Open, semi-open
Premalignant	
Actinic keratosis	Open
Malignant	
Pigmented BCC	Open, close
Lentigo malignant	Open

Seborrheic keratosis (SK)

Cryosurgery is probably the first treatment option in SK.⁹ It allows treating one or multiple lesions in one session, whether traumatized or not. Lesions can be frozen and left for spontaneous sloughing. Another option is to freeze them and then curette them off during thawing. This latter procedure will shorten the healing process. When considering curettage, keep in mind that once thawing is completed, there will be a reactive postoperative bleeding that will need to be stopped with topical hemostatic substances like 20%–30% trichloroacetic acid, Monsel's solution, or 20%–70% aluminum chloride.

The time required will depend on the size and thickness of the lesion. The lesion needs to be frozen completely, and 1 mm of peripheral healthy skin should be included to avoid recurrences in the outer border.

For large lesions, it is best to do segmental cryosurgery. This consists of treating a large lesion as if it was a sum of several small ones. If one tries to freeze a large superficial lesion in one session starting at the center, by the time the freezing front reaches the periphery, there will be excessive destruction at the center of the lesion and eventually an unaesthetic scar.

One freeze–thaw cycle is sufficient. For a small, less than 1 cm lesion, 5 seconds might be sufficient. Numerous lesions can be treated in one session (Figure 32.2).

Postoperative care

No special care needs to be taken. Daily cleaning with water and soap (while showering) is sufficient followed by a disinfecting solution. For large lesions, some antibiotic ointment can reduce chances of infection.



Figure 32.1 Cryoshaving the cutaneous horn on the right thumb.



Figure 32.2 Cryosurgery (open technique, one cycle) on multiple pigmented SK of the scalp on an 82 year old patient.

For lesions in the face, the total healing time is around 7–10 days; for the torsum, 2–3 weeks; in lower extremities, 4–6 weeks.

Postsurgical sun protection is important to avoid hyperpigmentation.

Lentigo simplex, ephelides

Lentigos simplex, solaris, and ephelides represent a common cause of consultation. One single session of cryosurgery is sufficient, using spray (open) technique. For very small lesions, the use of otoscope specula tips can help restrain LN to the desired area of treatment and avoid freezing healthy skin. Intermittent spraying gives more precision.

For a 5 mm lesion, 2–3 seconds freezing can be sufficient. It is important to freeze slightly over the edge (Figure 32.3).

Postoperative care

No special care is required. Daily cleaning with water and soap is sufficient. For larger lesions, an antibiotic ointment can reduce chances of infection. The first minutes after freezing the area will show a wheal; after 24 hours, the pigmented lesion will look darker and surrounded by a red-dish rim. For treatments in the face, complete lesion will slough off after 4–5 days, leaving a pinkish area that will last some weeks; in the dorsum of hands, it can take up to 3–4 weeks.

PREMALIGNANT LESIONS

Actinic keratosis

Cryosurgery is the first treatment option for actinic keratosis, including those hyperpigmented. Freezing needs to be around -15°C to -20°C . For a 7 mm lesion, this is



Figure 32.3 Cryosurgery (open technique, one cycle) on solar lentigos on the left cheek of a 77 year old female patient.

achieved after 10–15 seconds. Checkpoint tip: The frozen lesion should be palpable and grasped between fingers.

From the oncologic and cosmetic point of view, the best treatments combine topical field therapy of skin cancerization and local cryosurgical treatment of thicker, hyperkeratotic lesions (5-fluorouracil cream,¹⁰ ingenol mebutate,¹¹ imiquimod, and diclofenac sodium¹²).

Postoperative care

As freezing is deeper than with benign lesion treatment, there can be blister formation. No special postoperative care is required: daily water and soap washing, some anti-septic solution, and antibiotic ointment. For face lesions, healing will occur in approximately 10 days.

Field cancerization

Large areas of sun-damaged skin can be treated with cryopeeling (Figure 32.4). Previous local anesthesia by local anesthetic cream is required as this may be painful. Oral analgesic might also help in cold sensitive patients; 5–6 cm areas can be treated consecutively, spraying with acne tip (Brymill®) or a large aperture tip. Freezing should be superficial and rapid: no spraying from the center but with a brushing movement. Local anesthetic cream can be reapplied with thawing to reduce discomfort.

Postoperative care

Patients might feel some discomfort during and after treatment. Oral analgesic might be required. No other special postoperative care is necessary besides daily water and soap cleaning and antibiotic ointment. For scalp areas, healing will occur in approximately 10–15 days. Once the treated area has sloughed off completely, patients should start applying a hydrating/emollient cream. Postprocedural sun protection is extremely important.

MALIGNANT LESIONS

For selected BCCs and squamous cell carcinomas (SCCs), cryosurgery is an excellent therapeutic option. It offers

high cure rates and good to excellent cosmetic results. Tumors will need to be carefully selected: most BCCs including pigmented BCC, some well- and moderately differentiated SCCs, some lentigo malignas, and it can be considered in palliative setting.

Some anatomical areas give better results than others. Cryosurgery on the earlobes, nasal ali, and eyelids tends to give nice cosmetic results (Figure 32.5) while the front and cheeks might result in visible unaesthetic scars.

The criteria for *not* using cryosurgery are those for selecting Mohs surgery. These are

- Recurrent tumors
- Tumors with perineural, perivascular infiltration
- Morpheiform, sclerodermiform, micronodular BCC
- Previously irradiated tumors
- Ill-defined tumors
- Poorly differentiated SCC

In lentigo maligna, cryosurgery can be a good option for large cases that are inoperable, and results may be enhanced by treating them with immunocryosurgery, a combination of a topical immunomodulator with cryosurgery^{13–15} (Figure 32.6).

Skin cancer needs a double freeze–thaw cycle, preferably with close (probe) technique, which will reach faster and deeper. Probes need to match the tumor's size. In case of large lesions, segmental and fractional cryosurgery is an option. Spray technique is better for uneven surface tumors where regular probe fixation is not possible.¹⁶

Palliative treatment is to be considered any time we are in the presence of

- Malignant skin tumors in patients with underlying medical conditions where other therapeutic alternatives are not an option because of risk to patients' life (Figure 32.7).
- Bedridden, elderly patients; patients with mental conditions that make other therapies difficult.

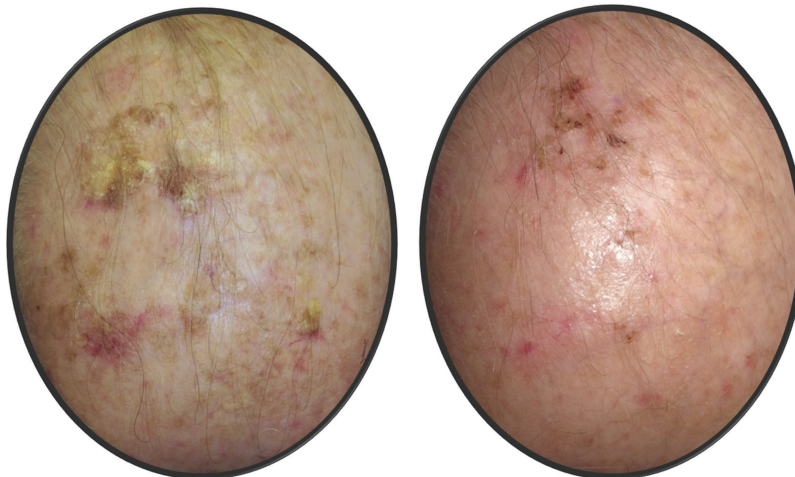


Figure 32.4 Cryopeeling on skin cancerization of the scalp of an 85 year old male patient.

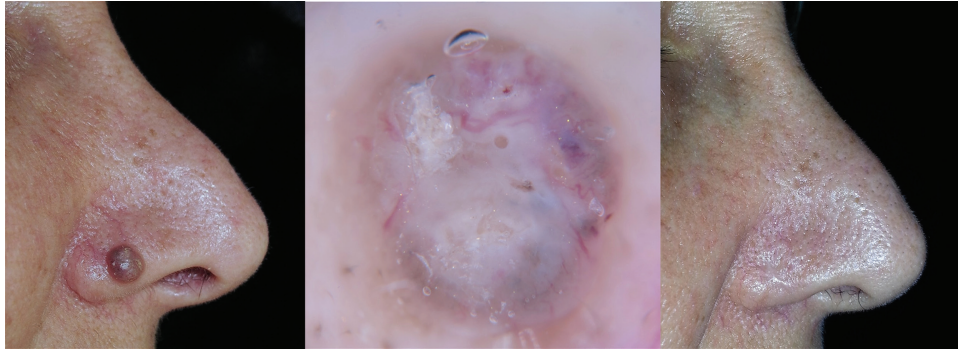


Figure 32.5 Double freeze–thaw cycle with close technique on a pigmented BCC on the right nasal ali of a 43 year old female patient.



Figure 32.6 Immunocryosurgery on a lentigo maligna melanoma on the right temporal zygomatic area on a 91 year old male patient.



Figure 32.7 Palliative treatment with double freeze–thaw cycle (close technique) on the left temple of a 95 year old female patient with a moderately differentiated SCC.

- Tumors that have not responded to other treatments. In irradiated skin, cryosurgery is not a contraindication, but healing may be more difficult.
- Patients/caretakers that refuse any other treatment alternatives (from fear, refusal to disfigurement, mobility difficulties to attend radiotherapy, etc.).

Palliation can also be applied to many pigmented conditions such as malignant melanomas or lentigo maligna melanoma.

WHERE NOT TO USE CRYOSURGERY

Patient and tumor selection is of extreme importance for any type of procedure.

In cryosurgery, darker skin types may heal with local hyperpigmentation even with superficial freezing; it is recommended to freeze a small hidden lesion before treating large areas, especially when treating benign lesions. Even in dark skin types, postoperative hypo- or hyperpigmentation might improve with time.

When treating skin cancer, freezing reaches deeper tissue. Residual scars can be hypopigmented or even achromic. Make sure patients are aware of this fact and accept it.

Melasma and other ill-defined hyperpigmented lesions should never be treated with cryosurgery.

POSSIBLE COMPLICATIONS

Any therapeutic treatment might have pitfalls. In cryosurgery, some expected occurrences like transient edema can be incorrectly interpreted as a side effect; however, extreme edema in cold sensitive skin should, in fact, be considered as one.

If a lesion has been previously shaved (for biopsy or to reduce keratin) or curetted, it can bleed profusely immediately after thawing. Hemostatic solutions should be at hand.

Pigmentation changes can occur, especially in deep freezing procedures and in darker skin types. It is usually transient, is rarely permanent, and tends to improve with time. Severely sun-damaged skin after healing might present an apparent hypopigmentation: it is, in reality, the normal skin color surrounded by hyperpigmented, sun-damaged skin.

Pain should be an important consideration. Some patients are more sensitive than others; cryosurgery may be more dangerous in certain anatomical areas (like fingers and feet) and better tolerated in others (face, posterior thorax).

Freezing with spray a previously curetted area can cause LN insufflation. This complication needs no medical intervention as it reabsorbs spontaneously.

In skin cancer treatment, there might be important scarring: lesions close to free margins are in high risk—tissue retraction in lower eyelids, notching or other defects for tumors close to the free margin of nasal alae or earlobes; depressed scars anywhere on the face or body; and alopecia

(temporary or permanent) on the scalp. Patients need to be previously informed of this possible side effect.

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INTRODUCTION

Electrosurgery (also known as radiosurgery and radiofrequency surgery) is a widely used modality in dermatologic surgery. Concentrating electrical current at the electrode–tissue interface using an unheated electrode allows precise carbonization, coagulation, and cutting. These surgical effects are achieved by converting high-frequency alternating electrical current (A/C) into heat. The basis of this technique relies on the highly resistive nature of living tissue. This allows the manifestation of Joule heating, which is a term to describe the diversion of kinetic energy to heat by collisions of accelerated charged particles with one another in a conductor. Modern electrosurgical units use transistors to create a multitude of frequencies and waveforms that can be optimized to treat various benign and malignant skin disorders.

TERMINOLOGY

Monopolar vs. bipolar

Electrosurgical units can be configured differently to provide specific effects. They can be classified as monopolar or bipolar, and monoterminal or biterminal. The term “polar” refers to the number of electrodes, whether active or return, that is in contact with the surgical site. A monopolar electrode (Figure 33.1a) usually comes in the form of a needle or ball-shaped tip that transfers concentrated electric current to the surgical site. Its effectiveness in cutting and coagulating tissues makes this modality a popular choice both in an office setting and in the operating room.

Bipolar configuration (Figure 33.1b) typically functions in the form of special forceps that contain both an active and a return electrode. Electrical current runs between the active and return electrodes, through the material in between, forming a complete circuit. It eliminates the requirement of using a patient return electrode. It is also more effective in a wet surgical field compared to the monopolar configuration. This method is generally considered safer as electrical sparks are less likely to occur and a lower voltage is required, which can limit collateral tissue destruction. However, it is typically harder to use and is not as effective at coagulating larger bleeding vessels due to its lower power output.

Monoterminal vs. biterminal

The term “terminal” refers to the number of connections between the patient and the electrosurgical unit. Monoterminal electrosurgery uses an active electrode with the return electrode connected to the earth rather than to the patient. Thus, all conductive materials around

the patient, including metal parts of the patient table or the physician’s non-insulated fingers, may act as an alternative pathway to complete a circuit. For this reason, all monoterminal surgeries should be performed on conscious patients only because burns are a major risk. This is more extensively discussed in the Complications section. Biterminal electrosurgery (Figure 33.1c) uses a return electrode connected between the electrosurgical unit and the patient in the form of a flexible metalized polymer pad or a large metal plate. This allows the concentrated electric current at the surgical site to be dispersed over a large surface area, preventing a burn at the return electrode. Of note, bipolar forceps are a type of biterminal modality by definition as there are two connections between the patient and the electrosurgical unit.

Frequencies

Passing electricity through living tissues has many implications. Only certain frequencies of oscillating electric currents can be used to produce desirable effects while minimizing risk. In the United States, modern electrosurgical units convert the conventional 60 Hz electrical current to a high-frequency current up to a typical range of 0.3–5 MHz. This rate of oscillation falls within the radio-wave frequency in the electromagnetic spectrum, which is the reason why electrosurgery is also known as radiofrequency surgery. Lower frequency current in the hertz to kilohertz range is more prone to causing cell membrane excitation and muscle and nerve stimulation, and is thus not optimal for usage on human tissue.^{1–3} While the lower limit is set due to biological constraints, the upper limit is set for safety concerns. Ultra-high-frequency electric current can cause significant current leakage resulting in a burn if a patient or physician is in close contact with the wiring of the active electrode. It can also reduce the efficiency of the electrosurgical unit if the wirings of the active and return electrodes are in close proximity.⁴

PREOPERATIVE EVALUATION AND PREPARATION

Preoperative evaluation must include an assessment of the patient’s risk factors for the procedure and potential safety concerns for the surgical team. Potential risk factors for undergoing electrosurgery include the following: the presence of cardiac implantable electronic devices (IEDs), chronic medical conditions that would impair wound healing or require preoperative antibiotics, anticoagulation status, transmittable diseases, and allergic reactions to anesthetics. Patients with implantable cardioverter defibrillators (ICDs) and pacemakers must be carefully assessed for potential risks of interference. This is discussed more extensively in the Complications section.

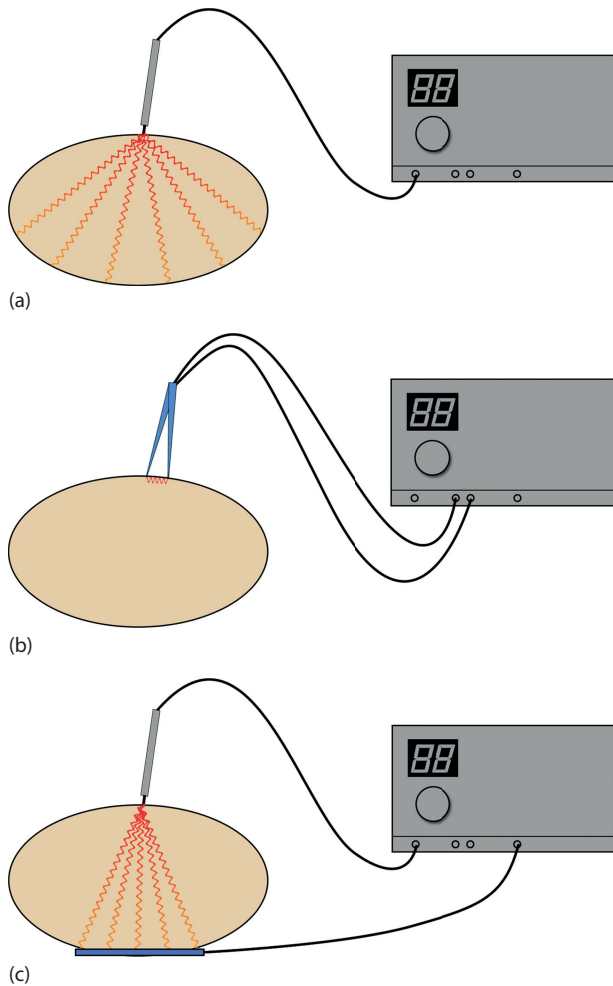


Figure 33.1 (a) Monopolar electrode. (b) Bipolar configuration. (c) Biterminal electrosurgery.

Protective gear for the surgical team to prevent hazard exposure is of utmost importance. Facemasks and eye shields should be worn to protect against blood and fluid splatter as well as the surgical smoke plume that may contain carcinogens and viral particles. Both general room ventilation and local exhaust ventilation devices should be used to protect against chronic smoke exposure. Surgical gloves must also be worn.

Depending on the location and the type of surgery performed, no anesthetics, topical and local anesthetic, or nerve blocks can be done. One percent lidocaine with 1:100,000 epinephrine is most frequently used for outpatient office-based surgeries. Prior to the beginning of the surgery, the patient must be positioned on an insulated surgical table to prevent electrical burns. This is further discussed in the Complications section.

ELECTROCAUTERY

Electrocautery (from Latin, *cautērium*, branding iron) is one of the earliest forms of surgical techniques that involves the use of electricity and Joule heating for treating skin lesions. Although it uses the same principles of

electricity, it is distinctly different from modern electrosurgery. As opposed to electrosurgery where high-frequency alternating current passes through the tissue, electrocautery describes the method in which direct current is used to heat up a metal element, similar to that of an electric coil stove. The hot element is then placed on the surgical site to cause thermal destruction or cauterization of the tissue. Since electrocautery does not involve passing electricity through the patient, it is a preferred method in special situations such as surgeries on patients with pacemakers and ICDs. However, in most other cases, electrosurgery is the preferable technique as it is generally more effective and produces less collateral thermal damage for improved healing and scar formation.

TYPES OF ELECTROSURGERIES (FIGURE 33.2 AND TABLE 33.1)

Electrodesiccation and electrofulguration

Electrodesiccation (from Latin, *dēsiccatūs*, dried up) and electrofulguration (from Latin, *fulgurāre*, lightning) are commonly performed procedures by dermatologists in an office-based setting for the treatment of very superficial lesions. These involve the use of a markedly damped, high-voltage, and low-amperage current in a monoterminal configuration. Since the patient is not connected to a patient return electrode, electric current accumulates within the patient. Thus, a high voltage is required to establish a continuous flow of current.⁵ Since Joule's first law indicates that energy released is proportional to the square of the current ($Q = I^2Rt$), a low current is used to prevent extensive destruction of superficial tissue. Electrodesiccation is a method that contacts the skin with the electrode to vaporize the water content in the cells, thus dehydrating the superficial tissues.

Electrofulguration is a similar technique where the electrode does not come in direct contact with the skin. Instead, the electrode is typically held 1–2 mm above the lesion. Air molecules between the electrode and the patient's skin are ionized by the electric current, forming an electric arc similar to that of naturally occurring lightning. The arc may not form directly under the electrode at all times and may flicker to surrounding areas. This causes superficial dehydration and carbonization over a wider area compared to electrodesiccation. Dehydrated or carbonized tissues are poorer conductors of electricity, which help prevent more extensive damage to deeper tissues. These methods typically provide excellent healing and minimal scar formation if low power is used.

Electrodesiccation and electrofulguration are generally used to treat superficial lesions including lentigines, dermatosis papulosa nigra (DPN), and seborrheic keratoses. Electrofulguration is ideal for treating lentigines because its thermal damage is contained at the superficial skin layers. The spark formed between the electrode–tissue interface also flickers, which allows larger treatment area compared to electrodesiccation in the same amount of time. Low-powered electrodesiccation can be used to

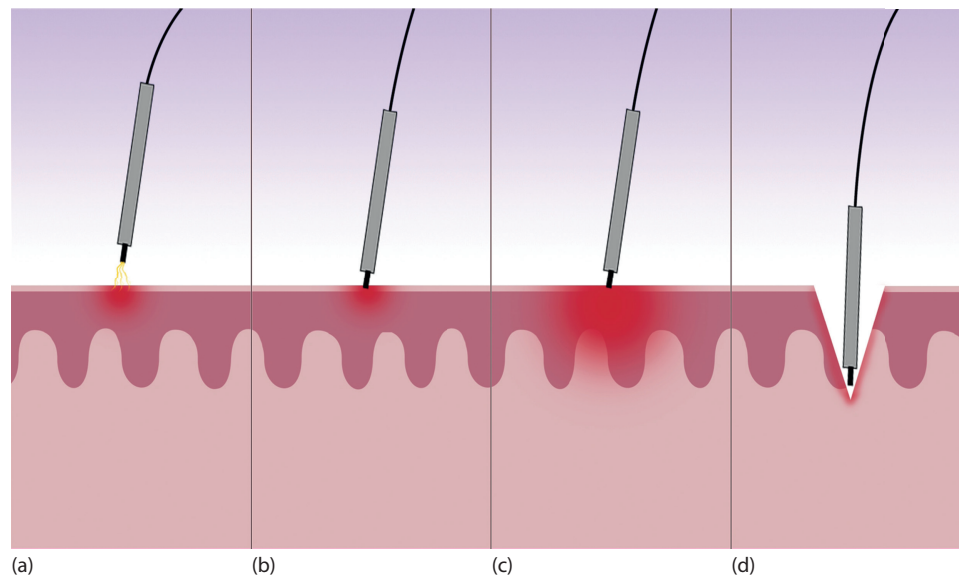


Figure 33.2 Types of electrosurgery: (a) electrofulguration; (b) electrodesiccation; (c) electrocoagulation; and (d) electrosection.

Table 33.1 Types of electrosurgery.

Modality	Electrodesiccation	Electrofulguration	Electrocoagulation	Electrosection
Waveform	Markedly damped	Markedly damped	Moderately damped	Slightly damped/ undamped
Configuration	Monoterminal	Monoterminal	Biterminal	Biterminal
Voltage	High	High	Low	Low
Current	Low	Low	High	High
Frequency	High	High	High	High
Electrode position	Physical contact	No physical contact	Physical contact	Physical contact

treat small DPNs to prevent side effects such as hyperpigmentation. Larger DPNs and seborrheic keratoses can be treated either with electrodesiccation or in combination with curettage. Electrosurgery is not recommended for the destruction of melanocytic lesions as a tissue specimen cannot be obtained and the scarring can affect future histopathologic analysis.

Electrocoagulation

Electrocoagulation (from Latin, *coāgulāre*, curdle) is an ideal modality for treating deeper skin lesions, including certain cutaneous malignancies, and to obtain hemostasis. It uses a moderately damped, low-voltage, and high-amperage current in a biterminal configuration. Unlike the monoterminal modalities, the use of a patient return electrode allows the formation of a complete circuit and prevents current accumulation in the patient. This enhances the efficiency of the system; thus, a low voltage is sufficient to maintain the current flow. As noted above, current is an important factor in Joule heating to determine the energy delivered to the tissue. Thus, high amperage used in electrocoagulation can cause deep tissue destruction and hemostasis by collagen denaturation. Hemostasis can be obtained by touching the electrode directly onto the

bleeding vessel, indirectly touching the electrode to the forceps that is clamped onto the vessel, or clamping the vessel with bipolar forceps. Prolonged electrocoagulation will cause the surrounding tissue to desiccate or carbonize, which reduces its conductivity and limits collateral heat damage. This modality causes deeper tissue destruction and will create more scar formation compared to the monoterminal modalities.

Electrosection

Electrosection (from Latin, *sectiōn*, cutting) is used for excising or debulking skin lesions and performing effortless skin incisions. It uses a slightly damped or undamped, low-voltage, and high-amperage current in a biterminal configuration. The high amperage used allows a large energy transfer to the tissue, which causes vaporization of the tissues, resulting in the cutting effect. In the “blend” mode, cutting and hemostasis can be simultaneously achieved, albeit requiring spot electrocoagulation for larger bleeding vessels. For the best cutting effect with the least amount of collateral tissue damage, the “pure” cutting mode should be used. Despite its effectiveness in incisions and excisions, it creates histologic artifacts from collagen denaturation and carbonization at the margins.

Thus, when it is necessary to assess the margins of the specimen histopathologically, such as in the case of malignancy excisions, a scalpel would be the preferred modality.

SAFETY CONCERNS

Cardiac pacemakers/ICDs

Encountering patients with cardiac pacemakers and ICDs is becoming more common. It is often a concern regarding the use of electrosurgery in patients with IEDs and their potential side effects. There have been multiple reports in the past describing interference of the IEDs by electromagnetic interference (EMI) generated from the electrosurgical devices. This can potentially become a life-threatening complication as these IEDs misinterpret the signals and malfunction. Pacemakers may pause when EMI causes oversensing, leading to arrhythmias. EMI detected by ICDs can also erroneously be interpreted as tachyarrhythmias, leading to inappropriate shocking. The location of the surgery is also important as the risk of IED malfunction due to EMI increases near the heart.^{6–10} Although modern pacemakers and ICDs have improved shielding from EMI and filtering systems, preventive measures or alternative treatment options must be carefully considered. Patients with pacemakers and ICDs should have undergone routine device maintenance within the past 12 and 6 months, respectively. Pre- and postsurgery device evaluation may be required when monopolar biterminal electrosurgery is performed in close proximity to the IED. Cardiac consultation may also be required if high-energy electrosurgical procedures are planned. Although not universally required, some institutions suggest reprogramming to an asynchronous mode in pacemaker-dependent patients prior to the surgery.^{11–14} An alternative of monopolar electrosurgery is the usage of a bipolar modality. Since electric current travels from the active electrode directly to the return electrode at the surgical site, EMI is minimal. Electrocautery is also an excellent alternative as no electricity passes through the patient, and there is an extremely low risk in causing IED malfunction.

POSTOPERATIVE MANAGEMENT

Optimizing postoperative care is essential for good wound healing and cosmetic outcomes. Minor procedures such as superficial skin lesion ablation or standard electrodesiccation and curettage procedures require only the application of topical petrolatum for several days. More extensive wounds require a longer healing time. Applying topical petrolatum and antibiotic ointment with occlusive dressing can keep the wound moist, which facilitates keratinocyte migration and collagen matrix deposition. This aids in the speed and quality of wound healing. Although topical antibiotics are commonly used, many studies have found no improved efficacy compared to petrolatum-based ointment alone.^{15–17} Furthermore, antibiotic ointments, such as neomycin and bacitracin, frequently cause allergic contact dermatitis. Therefore, for clean electrosurgical procedures, plain petrolatum ointment is recommended for superior safety profile and equivalent outcomes.

COMPLICATIONS

Dyschromia and scarring

Insults to the skin, whether from trauma, disease processes, or iatrogenic causes, may cause changes in its integrity. Inflammatory response occurs as the skin surface is damaged, which can lead to post-inflammatory hyper- or hypopigmentation, as well as scarring. Individuals with darker skin tones are more susceptible to post-inflammatory hyperpigmentation. Although the exact mechanism of post-inflammatory is unknown, several potential cellular processes may play a role. Stimulation of melanocytes by inflammatory cytokines such as interleukin-1 α , reactive oxygen species such as superoxide and nitric oxide, inflammatory mediators including prostaglandins, as well as α -melanocyte stimulating hormones may be responsible for the hyperpigmentation.^{18–22}

Post-inflammatory hypopigmentation also occurs more frequently in darker-skinned patients. Physical damage and the inflammatory response after the surgical procedure can disrupt melanocytes. This can cause a reduction in melanin production that is clinically seen as areas of decreased pigmentation. When injuries are limited to the epidermis or papillary dermis, healing without scarring can be expected. However, scar tissue will form if the skin insult extends to the reticular dermis.

Thermoelectric burn

Although the risk of severe burns is low in the outpatient setting since the electrosurgical unit generates very low power, precautions must be done to prevent this potentially severe morbidity. When a monopolar monoterminally office-based electrosurgical unit is used, such as the *Hyfrecator*[®] and equivalent machines, the patient must be conscious and positioned on an insulated table. Any metallic objects, including the metallic portion of the surgical table and even EKG leads, may act as a return electrode completing the circuit (Figure 33.3). Since these surgeries do not typically utilize a grounding pad, current accumulates in the patient. Accidental contact with these metallic objects can discharge the current accumulated through the connection. The electric current density may be high if there is a small contact surface area, and the high energy density can cause a spark and potentially a burn. A conscious patient will be able to feel pain and

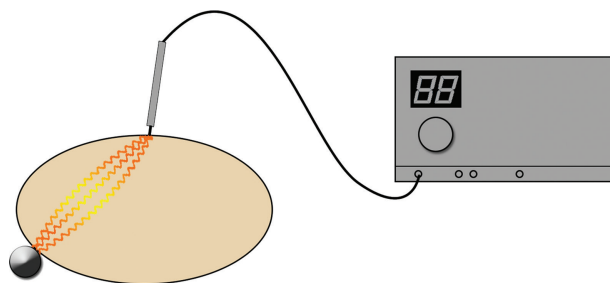


Figure 33.3 Monopolar monoterminally office-based electrosurgical unit.

notify the surgeon. However, if the patient is unconscious, extensive burns may result.

Care should also be taken when monopolar surgery is performed on thin extremities including fingers, toes, and penis. Although rare, prolonged usage in high power can potentially cause an elevated temperature due to the small cross-sectional area. The electric current may be sufficiently dense to cause thermal damage of the extremity.¹⁰

Smoke plume

Since electrosurgeries have become increasingly common in recent years, dermatologists must be aware of the cumulative effect of surgical smoke exposure. Thermal destruction of tissues releases smoke as a by-product. Electrosurgical smoke has been shown to contain hydrocarbons, nitriles, phenols, carbon monoxide, and hydrocyanide. Short-term exposure to these molecules may cause eye irritation, nausea, vomiting, lightheadedness, and headache. However, long-term exposure may lead to higher incidence of cancer.^{23,24} Apart from these potentially harmful molecules, numerous studies also confirmed the presence of a variety of bacteria and viruses including HIV and HPV.^{25,26}

Research by the National Institute for Occupational Safety and Health (NIOSH) has shown that exposure to these by-products can be effectively minimized. A combination of general room and local exhaust ventilation (LEV) systems is recommended. LEV comes in two major forms—smoke evacuators and room suction systems. Smoke evacuators should have a capture velocity of 100 to 150 feet per minute at the inlet and be held less than 2 inches away from the surgical site. Installation of high efficiency particulate air filters in the ventilation system is recommended. Room suction systems are used to evacuate any remaining particles from the procedure room. Apart from adequate ventilation, the surgical team should be equipped with individual respiratory protection such as N-95 or other NIOSH-approved respirators.²⁷

Fire

Since electricity is involved in these procedures, one has to be cognizant about flammable substances that may be in contact with the surgical field. Alcohol wipes are often used in outpatient office procedures for cleaning the skin before minor electrosurgery. Not allowing the alcohol to dry completely before introducing electricity on the skin may potentially cause a fire. Aluminum chloride is also a flammable chemical used for hemostasis. Bowel gas containing methane is a fire hazard since it is extremely flammable, and care should be taken while working in close proximity to the perianal area.

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INTRODUCTION

Hyperpigmentation of the skin is caused by a variety of endogenous and exogenous skin conditions and injuries. The degree of hyperpigmentation is influenced by the underlying cause as well as skin type. Darker-skinned patients can have a predisposition to more pronounced and longer-lasting hyperpigmentation of the skin. When evaluating a patient for the treatment of hyperpigmentation, it is important to consider the mechanism of the hyperpigmentation, the duration of the hyperpigmentation, and the patient's skin type.

The leading causes of hyperpigmentation of the skin include melasma, photoaging, nevus of ota, post-inflammatory hyperpigmentation (PIH), and other inflammatory conditions of the skin. The degree of pigment deposition varies in each of these conditions. It is important to divide pigmented lesions into epidermal and dermal lesions, as different treatment strategies are employed based on the depth of the pigmentation. In epidermal lesions, the pigment is situated in the epidermis or at the dermoepidermal junction, and in dermal lesions, the pigment extends into the dermis.¹ A Wood's lamp can help distinguish between epidermal and dermal lesions, as epidermal lesions illuminate more under the Wood's lamp than dermal lesions and epidermal hyperpigmentation is more responsive to treatment.² Of note, a Wood's lamp is more useful in Fitzpatrick skin types I–III and less useful for darker-skinned patients.³

Disorders of pigmentation commonly affect patients of Fitzpatrick type III and above, possibly due to more hyperreactive melanocytes in these patients.³ Treatment of hyperpigmentation in skin of patients of color can be difficult as the treatments can cause more irritation and lead to further hyperpigmentation. Thus, special consideration must be made for darker-skinned patients.

A significant impact on the quality of life is found in patients with hyperpigmentation of the skin. In patients with melasma, a review by Pawaskar et al.⁴ showed that melasma caused emotional distress owing to its location on the face and disfiguring nature and negatively affected social functioning in Hispanic women. Treatment of melasma can improve the quality of life of individuals.⁵ Thus, it is essential to utilize effective treatments for hyperpigmentation as treatment can lead to large improvements in an individual's overall well-being.

The treatment of hyperpigmentation of the skin includes hydroquinone, chemical peels, cryotherapy, and laser therapy. We will be focusing on treatment of hyperpigmentation with laser therapy in this chapter. The acronym LASER stands for light amplification by the use of

stimulated emission of radiation. Laser light has several properties that distinguish it from different light sources. First, lasers use monochromatic emitted light, or light of one wavelength. The light is coherent, meaning that the light travels in phase in time and space, and laser light is collimated and can travel long distances in a parallel beam.⁶ Lasers target specific chromophores of the skin, including melanin, hemoglobin, and water. Each of these chromophores absorbs certain select wavelengths of light.

There are several principles to consider when treating cutaneous skin lesions with laser therapy. Each chromophore in the skin has a specific thermal relaxation time (TRT), which is the time for the heated target chromophore to return to half of its initial temperature.⁷ The TRT is shorter for smaller chromophores, such as tattoo pigment, rather than for larger chromophores, like a capillary. The TRT can be approximated by the square of the target chromophore diameter, or $TRT \sim d^2$.⁶ Another key principle of laser therapy is the principle of selective photothermolysis by Anderson and Parish,⁸ which states that focal local destruction of the target tissue can be achieved by a laser that emits the specific wavelength that is absorbed by the target tissue at a pulse duration that is approximately equal to or shorter than the TRT of the tissue. By selectively targeting the chromophore, adjacent tissues are spared and the risk of side effects is minimized. Thus, in the instance of targeting melanin pigment, the laser wavelength should be equal to the absorption spectrum of the laser at the pulse duration equal to half of the TRT to target melanin.

Another key development in the use of lasers for cutaneous lesions is the concept of fractional photothermolysis (FP) introduced by Manstein and Anderson in 2004. FP differs from other laser modalities in that it involves the placement of numerous microscopic zones of thermal damage, leaving the majority of skin tissue intact as a reservoir for healing. No open wounds are left following treatment allowing for minimal downtime for patients.⁹

Preoperative preparation before using laser is essential. Contraindications to the use of laser therapy include use of isotretinoin in the past 6 months, active infections such as hepatitis C, and pregnancy.¹ It is important to perform preoperative and postoperative prophylaxis when using ablative laser procedures with antiviral medications, such as valacyclovir or acyclovir, and antibiotics to avoid reactivation of herpes viruses and bacterial overgrowth on the skin. Providers should also take precautions and use masks for ablative lasers. In addition, patients should avoid the sun several weeks prior and after the laser procedure to prevent side effects of dyschromia. The provider and the

patient should use appropriate eye protection depending on the wavelength of the laser.

MELASMA

Melasma is a chronic, acquired disorder of hyperpigmentation characterized by symmetric brown macules over sun-exposed areas of skin, usually on the face. Although it may affect both sexes and all races, it is more commonly seen in females of intermediate skin pigmentation (Fitzpatrick skin types III–V).^{10,11} The exact pathogenesis of melasma is unknown, although ultraviolet (UV) radiation exposure appears to exacerbate the condition.¹² Although melasma is a common and benign disorder, the demand for treatment is high due to aesthetic concerns and psychological impact on the patients affected.

Various modalities have been used to treat melasma, but recurrences are common, making it difficult to cure. Lasers that have been studied for the treatment of melasma include Q-switched lasers (alexandrite, ruby, and neodymium-doped yttrium aluminum garnet) and fractional lasers. The target chromophore of these lasers in the treatment of melasma is melanin. Q-switched lasers are used because melanin is a very small chromophore with a short TRT, and these lasers can provide the very small pulse duration needed to meet the small TRT of melanin and destroy the chromophore.

There are two types of Q-switched neodymium-doped yttrium aluminum garnet (QS Nd:YAG) lasers: frequency-doubled (532 nm) and nonfrequency-doubled (1064 nm). The nonfrequency-doubled 1064-nm QS Nd:YAG is the most common laser used for the treatment of melasma. Laser toning using a 1064-nm QS Nd:YAG laser has been reported to be effective in the treatment of melasma. Treatments occur at 1-week intervals for 5–10 sessions using a fluence of less than 5 J/cm², spot size 6 mm, and frequency of 10 Hz.¹³ Choi et al.¹⁴ treated 20 melasma patients (mean age 39.5, 19 females and 1 male, Fitzpatrick skin type III–IV) with a 1064-nm QS Nd:YAG laser using a fluence of 2.0–3.5 J/cm², spot size of 6 mm, and repetition rate of 10 Hz for five treatments at 1-week intervals. Two regions on each patient were assessed 4 weeks following the last treatment and showed statistically significant lightening of the skin and decrease in the melanin index of the melasma lesions. No complications of dyschromia were noted during or after the treatment. By delivering repetitive energy with a subtherapeutic fluence, it is thought that melanin granules are fragmented and dispersed into cytoplasm without causing cellular damage or cell death. This method has been shown to be effective for lightening both epidermal and dermal melasma. However, due to the frequency of recurrence with melasma, prevention with broad-spectrum sunscreens and topical tyrosinase inhibitors following laser therapies is recommended. Transient reactions from QS Nd:YAG lasers may occur including immediate erythema, physical urticarial, acneiform eruption, minute petechiae, and whitening of fine hair. Serious complications justifying suspension of treatment include mottling hypopigmentation, leukoderma,

severe urticarial, severe acneiform eruption, and herpes simplex activation.¹⁵ See Figure 34.1.

Q-switched alexandrite lasers (QSAL) and Q-switched ruby lasers (QSRL) have been used in the treatment of melasma with variable success rates. In a study conducted by Fabi et al.,¹⁶ 20 patients with moderate to severe mixed-type melasma received treatment with both low fluence QSAL (755 nm) on one half of their face and low fluence QS Nd:YAG (1064 nm) on the other half of their face. Of the 16 that completed the study, both sides of the face showed significant improvement in the Modified Melasma Area and Severity Index (mMASI) score without significant difference between the two groups. It was noted that the QSAL required fewer passes than the QS Nd:YAG laser to achieve mild erythema. However, careful use of the QSAL laser is required to prevent overlapping or accidentally pulse stacking, which could lead to a greater risk of overstimulating melanocytes compared to QS Nd:YAG lasers.¹⁶ Earlier studies reported QSRL as an ineffective treatment modality for melasma with potential worsening of melasma and/or development of PIH.^{17,18} However, Hilton et al.¹⁹ performed a retrospective study evaluating the effectiveness of fractional-mode

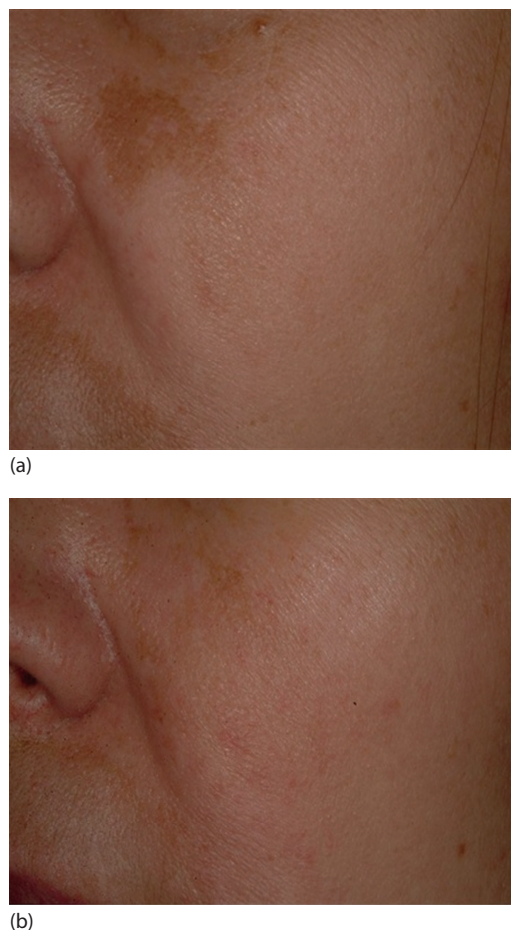


Figure 34.1 Melasma (a) before and (b) after treatment by QS-Nd:YAG, 0.9 J/cm², 6 mm, 5–10 ns. (Courtesy of Jerome M. Garden MD and Abnoel D. Bakus PhD.)

QSRL in the treatment of 25 Caucasian melasma patients. Fractional-mode QSRL (694 nm) was used at fluences of 4 to 8 J/cm² and a frequency of 1 Hz for up to three sessions (average of 1.4). Fractional mode was used to minimize adverse effects previously seen with classical QSRL. Significant reduction in Melasma Area and Severity Index (MASI) scores was evident at 4 to 6 weeks following the last laser treatment. However, after 3 months, PIH and/or recurring melasma were observed in 7 (28%) and 11 (44%) patients, respectively.¹⁹

Non-ablative fractional lasers at wavelengths of 1540 and 1550 nm have been suggested for the treatment of melasma.²⁰ Earlier studies reported improvement in the appearance of melasma lesions following fractional non-ablative laser therapy.^{20–22} However, further studies evaluating non-ablative FP have noted no change or worsening of lesions in Fitzpatrick skin type IV individuals,²³ similar efficacy in improvement of lesions compared to sunscreen alone,²⁴ and similar efficacy in improvement of lesions compared to hydroquinone-based triple topical therapy.²⁵ Recurrence following fractional non-ablative laser therapy as well as side effects including erythema, burning sensation, facial edema, and pain have also been noted. PIH has been reported as a complication, which may be exacerbated by using a higher energy per microbeam settings.²⁶

Ablative lasers have also been studied for the treatment of melasma. Two lasers that have been evaluated are the erbium-doped yttrium aluminum garnet (Er:YAG) laser (2940 nm) and the fractional carbon dioxide (CO₂) laser (10,600 nm). Wanitphakdeedecha et al.²⁷ conducted a study on 20 Thai women with melasma using the Er:YAG laser. Although initial results demonstrated significant improvement in melasma, recurrence was noted after discontinuation of treatment.²⁷ High-power fractional CO₂ lasers have been evaluated in the past with some success, but their use has been cautioned due to increased risk of PIH.²³ A recent split-face study by Jalaly et al.²⁸ compared the efficacy of low-power fractional CO₂ to low-fluence QS Nd:YAG laser therapy. Forty patients were treated at 3-week intervals for five consecutive sessions. Patients demonstrated significant reduction in the melanin index and mMASI score with a significantly larger reduction in both on the side of the face that was treated with low-power fractional CO₂ laser.²⁸

Further studies have evaluated the use of lasers and topical therapies together. Jeong et al.²⁹ treated 13 patients with a 1064-nm QS Nd:YAG laser before and after 8-week therapy with triple combination (TC) cream (4% hydroquinone, 0.05% tretinoin, 0.01% fluocinolone acetonide). MASI score reduction at 16 weeks was greater in the patients that received TC cream followed by laser treatment compared to the group that received laser treatment followed by TC cream.²⁹ In another study, Trelles et al.³⁰ demonstrated initial improvement with fractional CO₂ lasers alone, hydroquinone-based triple cream alone, and fractional CO₂ laser in addition to hydroquinone-based triple cream. However, long-term benefits were maintained best when both hydroquinone-based triple cream

and fractional CO₂ laser were used in combination compared to either alone.³⁰

Melasma is a difficult disorder to treat, and different treatment modalities have variable success rates. Although success has been shown with some laser therapies, the risk versus benefit must be addressed when considering such treatment options for patients. Low-fluence QS Nd:YAG lasers appear to have a lower risk of side effects, although caution must still be exercised. Future studies may help discern the effectiveness of newer laser therapies such as low-power fractional CO₂ lasers. Due to the high recurrence rates, combined topical therapy is recommended to help maintain laser treatment results. Additionally, regular broad-spectrum sunscreen use is crucial to prevent further exacerbation from UV radiation exposure.

PHOTOAGING

Solar lentigines are considered an early sign of photoaging. Although these lesions are benign, it is important to differentiate them from other pigmented lesions such as melanoma. Solar lentigines are flat brown to dark brown macules ranging from millimeters to centimeters in diameter. They are most frequently found on chronic sun-exposed areas (face, dorsum of hands, forearms) and are more common after age 50.³¹ Unlike ephelides, their pigmentation is not affected by different seasons.³²

Laser therapy is an effective treatment modality for solar lentigines with improvement typically noted after one treatment. Melanin is the target chromophore. Since the pigment is located in the epidermis, more superficially penetrating lasers are typically used including Q-switched lasers (ruby, alexandrite, and frequency-doubled QS Nd:YAG). Other lasers that have been evaluated for the removal of lentigines include CO₂ lasers, argon lasers, and long pulse alexandrite lasers (LPAL).

The QSRL emits visible red light at a wavelength of 694 nm. The recommended settings include a spot size of 6.5 mm and fluency of 3–5 J/cm². Most lentigines will clear after one to three treatments with the QSRL. Adverse effects include transient hypopigmentation and, rarely, depigmentation.³³ See Figure 34.2.

The QSAL and LPAL operate at a wavelength of 755 nm. The longer wavelength allows for deeper tissue penetration and less unwanted hypopigmentation compared to QSRL. Long pulse lasers have been thought to have fewer side effects. They cause tissue destruction purely by photothermolysis, whereas Q-switched lasers cause both photothermal and photomechanical effects due to their short burst of high energy radiation. It is thought that these photomechanical effects induce damage to surrounding oxyhemoglobin and melanin resulting in PIH.³³ Ho et al.³⁴ compared the efficacy of QSAL and LPAL in the treatment of solar lentigines and found significant improvement with both therapies with no statistically significant difference between the two. They also found higher rates of PIH and more severe pain, erythema, and edema with QSAL treatment.³⁴

The QS Nd:YAG laser operates at a wavelength of 1064 or 532 nm (frequency-doubled), pulse duration of



(a)



(b)

Figure 34.2 Lentigo (a) before and (b) after treatment by QS Ruby, 2.8 J/cm², 6.5 mm, 20–40 ns. (Courtesy of Jerome M. Garden MD and Abnoeal D. Bakus PhD.)

10–20 nanoseconds, spot size of 1.5–4 mm, and repetition rate of 1–10 Hz. Melanin has a strong affinity for 532-nm green light, whereas the 1064-nm wavelength penetrates skin more deeply but with a lower melanin absorption coefficient.³⁵ The frequency-doubled QS Nd:YAG (532 nm) has been more widely used for the treatment of solar lentigines due to its superficial penetration. Efficacy has been reported with one treatment, and higher fluences have been noted to produce higher clearance rates.^{36,37} Tse et al.¹⁸ compared the efficacy of QS Nd:YAG to QSRL and found a mean percent clearance of lesions of 67% with QSRL and 58% with QS Nd:YAG laser. See Figure 34.3.

The CO₂ laser emits light at a wavelength of 10,600 nm. Historically, CO₂ lasers have operated at continuous-wave settings and have been associated with high rates of adverse outcomes, such as scarring. However, lower doses and pulsed modes have been used to help reduce these complications. Dover et al.³⁸ reported the use of low-fluency CO₂ laser on five patients and found that 74% of lesions treated at 3.7 J/cm² and 81% of lesions at 4.4 J/cm² substantially lightened or cleared. Slight atrophic changes were present in two sites treated with 4.4 J/cm².³⁸ Low fluency is thought to induce thermal damage restricted to the epidermis with little to no damage to the underlying dermis.³⁹ Fitzpatrick et al.⁴⁰ compared the effectiveness of continuous-wave CO₂ laser to superpulsed CO₂ laser. All



(a)



(b)

Figure 34.3 Lentigines (a) before and (b) after treatment by QS-Nd:YAG, 1.3 J/cm², 6 mm, 5–10 ns. (Courtesy of Jerome M. Garden MD and Abnoeal D. Bakus PhD.)

83 lesions were completely removed in one treatment with either laser. The superpulsed CO₂ laser group had slightly less healing time compared to the continuous-wave CO₂ laser (2 weeks versus 2.5 weeks, respectively) and decreased incidence of scarring (25% versus 40%, respectively). For safe and effective results, they recommended using a superpulsed CO₂ laser with a pulse shorter than the TRT of skin (950 microseconds), pulse energy 250 mJ or higher, fluence of 4.75–19 J/cm², spot size ≥ 2mm, and repetition rate of 1–50 Hz.⁴⁰

Argon lasers emit a green or blue light at 488 and 514 nm, respectively. Stern et al.⁴¹ evaluated the effectiveness of continuous-wave CO₂ lasers, argon lasers, and cryotherapy in the treatment of solar lentigines. Although all three methods proved to be effective in lightening or clearing solar lentigines, cryotherapy was shown to be the most effective. However, grading of improvement was not standardized and was subject to variation in the judgments of the observers grading the photographs of the lesions treated.⁴¹

Lasers provide an effective treatment modality for solar lentigines. When opting for laser therapy, the benefits of treatment must be weighed against the risks of adverse effects including depigmentation and PIH. Superficial penetrating lasers are recommended to minimize such adverse effects. Any lesions concerning for malignancy should be biopsied. Additionally, photoprotection is encouraged since the risk of repigmentation is increased with UV light exposure.⁴²

NEVUS OF OTA

Nevus of ota is a benign congenital dermal melanocytic nevus that is usually located unilaterally in the V1 and V2 distribution of the face. This lesion occurs mainly in darker skin types, especially Asians, and predominantly in women.⁴³ While nevus of ota usually follows a benign course, patients should be followed closely as there are

rare reports of malignant melanoma developing in these lesions. In cases where nevus of ota involves the eye, there have been reports of glaucoma and uveal melanoma.⁴³ Other dermal melanocytosis includes the less common nevus of ito located on the posterior supraclavicular, scapular, and deltoid regions, and this lesion can be treated similar to nevus of ota.⁴⁴

The leading laser treatments for nevus of ota are Q-switched lasers, including Q-switched ruby, alexandrite, and Nd:YAG lasers. The target chromophore of nevus of ota is melanin, which is a very small chromophore with a TRT in the nanosecond range. Q-switch lasers produce very short pulses of energy in nanoseconds,⁷ and this short pulse duration limits thermal damage to the surrounding tissues and selectively destroys the target tissue of melanin within the dermal melanocytes.

The QSRL has a wavelength of 694 nm, which matches the target chromophore of nevus of ota's absorption spectrum of melanin. QSRL has been used since 1992 when Goldberg and Nychay⁴⁵ first successfully treated a nevus of ota with it. As nevus of ota usually occurs in patients with darker skin types, lower fluences are used to prevent complications of dyschromia. In a study by Ueda et al.,⁴⁶ 151 Japanese patients with nevus of ota were treated with

QSRL at a fluence of 5 J/cm² and a spot size of 6.5 mm every 2 months with a mean of about three treatments. The average age of the patients was 30 years, most were women, and there was a favorable response by 1 year of treatment. The number of treatments depended on the color of the nevus of ota, with blue-green lesions requiring more treatments than brown lesions. A retrospective study evaluating the long-term complications of QSRL showed that the most common complications were hypopigmentation in up to 16% of patients, and hyperpigmentation was seen in 5.9% of patients.⁴⁷ See Figure 34.4.

QSAL has a wavelength of 755 nm, and several studies have validated the use of QSAL for the use in the treatment of nevus of ota. In a retrospective study by Liu et al.⁴⁸ of 806 patients with nevus of ota that received a series of Q-switched alexandrite (755-nm wavelength) treatments, 93.9% had complete clearance of the lesion after a mean of 5.2 treatments at a fluence of 3.8 to 4.8 J/cm² using a 3-mm spot size after a 3-year follow-up period. The patients in this study were mainly women ranging in age from 7 months to 60 years, and after 3 years of follow-up, there were no reports of erythema, textural change, scarring, or dyschromia.

The Q-switch Nd:YAG laser (QS Nd:YAG) has a longer wavelength (1064 nm) than the QSRL and QSAL, which

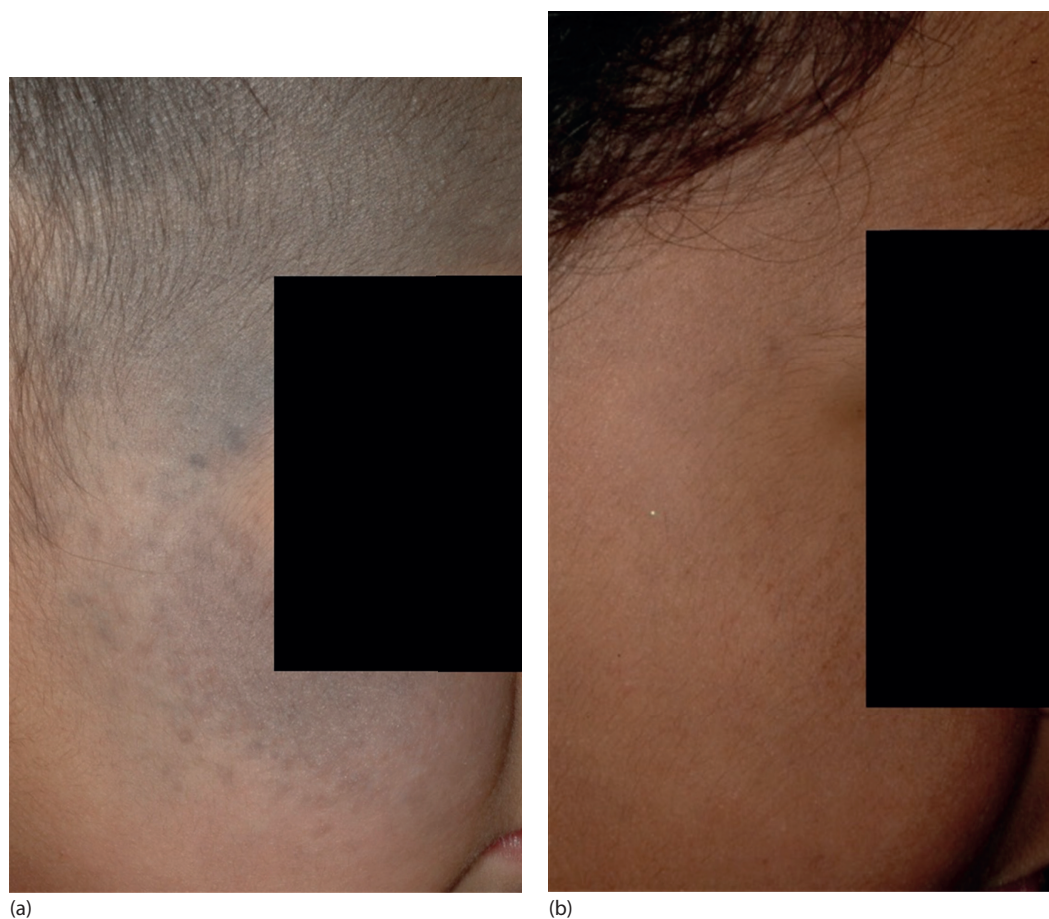


Figure 34.4 Nevus of ota (a) before and (b) after treatment by QS-Ruby, 2.3 J/cm², 6.5 mm, 20–40 ns. (Courtesy of Jerome M. Garden MD and Abnoeal D. Bakus PhD.)



Figure 34.5 Nevus of ota (a) before and (b) after treatment by QS-Nd:YAG, 1.0 J/cm², 6mm, 5-10ns (Courtesy of Jerome M. Garden MD and Abnoeal D. Bakus PhD).

allows deeper penetration into the dermis to target melanin with a lower risk of epidermal injury. However, this laser has less absorption of melanin and high fluences are required, which can cause more pain and potential for scarring.⁴³ While higher fluences have been used historically to treat nevus of ota with QS Nd:YAG, the trend now is to use lower fluences to prevent unwanted side effects. A retrospective study by Seo et al.⁴⁹ of 21 Korean patients with nevus of ota showed that using low fluences of 1.9 to 5.0 J/cm² in a 7- to 8-mm spot size, 96.8% reached improvement after a mean of 17 treatments. Adverse effects were minimal and dyschromia occurred in only one patient.⁴⁹ More treatment sessions were required with lower fluences, and the authors found that treating nevus of ota at an earlier age showed better results. See Figure 34.5.

POST-INFLAMMATORY HYPERPIGMENTATION

PIH is due to an excess of melanin pigment in the skin as a result of several inflammatory endogenous and exogenous dermatological conditions that can persist for several weeks to years.⁵⁰ This inflammation is thought to disrupt the epidermal–dermal junction leading to accumulation of melanophages in the upper dermis. In addition, arachidonic acid and other inflammatory markers are thought to stimulate melanin synthesis in the epidermis.⁵¹ PIH is more common in patients of skin of color and can occur anywhere on the body.

Several laser therapies have been employed to treat PIH with variable efficacy. Treatment with low fluence Q-switched Nd:YAG 1064-nm laser has been shown to improve PIH (see Figure 34.6).⁵² In this study, five patients

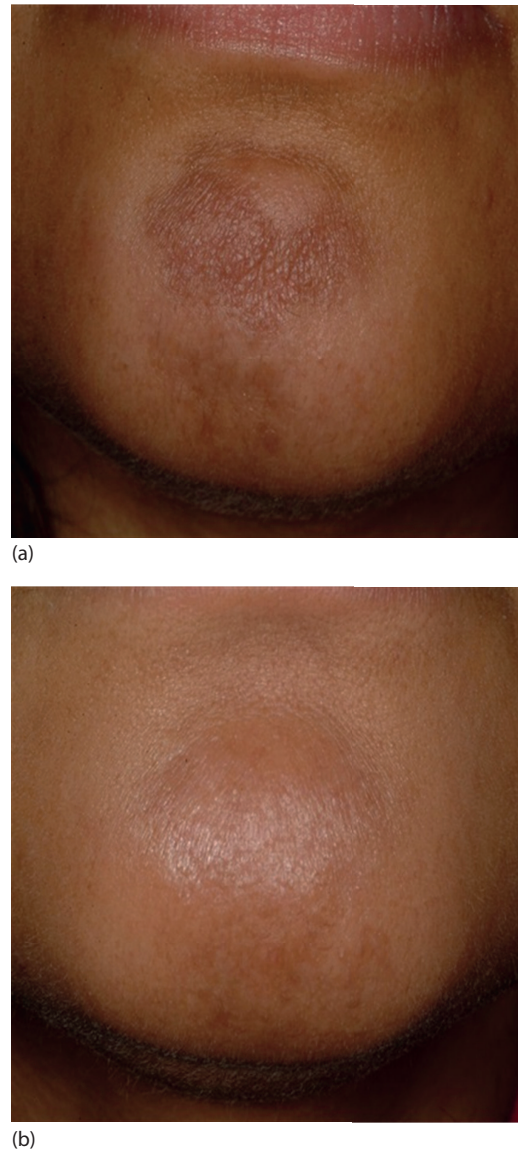


Figure 34.6 Post-inflammatory hyperpigmentation (a) before and (b) after treatment by QS-Nd:YAG, 1.1 J/cm², 6 mm, 5–10 ns. (Courtesy of Jerome M. Garden MD and Abnoeal D. Bakus PhD.)

with PIH on the face were treated with 5–10 sessions of low fluence 2.6–3.0 J/cm² with a 6-mm spot size and had significant improvement in PIH 3–6 months post final treatment without complications. The Q-switched 694-nm ruby (QSRL) has been used with varying degrees of success. Tafazzoli et al.⁵³ showed 75%–100% improvement in post-sclerotherapy hyperpigmentation with one to three treatments spaced 2–3 months apart of QSRL with a spot size of 4 mm and a fluence of 5.6–10.5 J/cm² in eight patients. However, Taylor et al.¹⁷ treated refractory melasma and PIH in eight patients with QSRL at fluences of 15–7.5 J/cm² without improvement in pigmentation. Fractional thermolysis has also been employed for the treatment of PIH in a woman with Fitzpatrick skin type of IV for a hyperpigmented patch on the neck.⁵⁴ A 1550-nm erbium-doped

Fraxel SR 1500 laser was employed for three treatments at 4- to 8-week intervals, and each treatment included 8–10 passes at a density of 110 MTZs/cm² per pass with near complete resolution of the hyperpigmentation.

It is always important to combine topical therapy with laser therapy for PIH and to advise patients to use strict sun protection with sunscreen and sun protective clothing. It is also necessary to treat the underlying inflammatory skin condition that caused the dyschromia to prevent further worsening of the dyschromia.

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Intense pulsed light

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WHAT IS INTENSE PULSED LIGHT?

Intense pulsed light (IPL) sources emit noncoherent, polychromatic (usually a wavelength range of 500–1200 nm) pulsed light to induce photothermal destruction of chromophores in the skin (Table 35.1). More precisely, IPL devices generate photons of energy, which are absorbed by chromophores, resulting in a transfer of energy that generates heat and subsequent destruction of the target structure.¹ IPL has been used in the treatment of a variety of cutaneous diseases (Table 35.2).

Multiple endogenous chromophores, including melanin, water, and hemoglobin, exhibit characteristic preferred absorption wavelengths. For example, melanin absorbs light continuously over a broad spectrum with peak absorptions at lower wavelengths.² This characteristic allows for preferential selection of chromophore destruction, or as Anderson et al. first coined the term, “selective photothermolysis.” Selective photothermolysis refers to the preferential targeting of pigmented structures based on their absorption spectrum of pulsed radiation. Ultimately, this technique allows for selective destruction of chosen pigmented targets with isolation of thermally mediated radiation damage that prevents injury to surrounding structures, an important principle that guides effective IPL therapy.³ Additionally, since IPL devices emit a spectrum of wavelengths, multiple chromophores can be activated¹; this is particularly important in diseases such as Poikiloderma of Civatte (POC), a disorder of both pigmentation and blood vessels, where one must target two chromophores, namely melanin and hemoglobin.⁴

IPL devices also utilize “cut-off” filters to deliver desired wavelength spectrums in order to achieve selective photothermolysis of certain components at different depths of the skin. The wavelength being delivered in IPL correlates directly with the depth of skin penetration; for example, longer wavelengths are able to penetrate deeper into the skin and are thus used to treat deeper targets while protecting and avoiding superficial parts of the skin. Conversely, shorter wavelengths are used to target more superficial targets while preserving and avoiding damaging deeper skin parts such as the dermis.^{3,5}

Moreover, IPL devices, like lasers, can utilize the concept of thermal relaxation time (TRT) to confine heat to a desired target with relative sparing of surrounding structures. TRT is related to the size of the target chromophore and represents the time taken for the target to dissipate about 50% of absorbed heat to surrounding tissues. The use of a pulse duration less than the TRT of the target is preferred in order to prevent excessive heat conduction to adjacent areas, thus preventing undesired thermal

damage.^{1,3} For example, by using a pulse duration of less than the TRT of melanosomes (70–250 nanoseconds), one should confine thermal damage to this chromophore and minimize risk of scarring.^{1,6} Finally, the ability to vary the many parameters in IPL, such as wavelength, fluence, pulse mode, duration, and delay, has contributed to the incredible versatility of IPL as a treatment modality; IPL may be used to treat vascular lesions such as telangiectasias and port-wine stains, pigmentation disorders such as melasma and POC, as well as other disorders that include acne vulgaris and hair removal (Table 35.2).

IPL AS A THERAPY FOR HYPERPIGMENTATION

IPL has been described in current literature as a therapy for the treatment of a variety of disorders of hyperpigmentation including melasma (level 1 evidence), lentigines (level 2 evidence), POC (level 3 evidence), nevus spilus, café au lait macule, Becker’s nevus, epidermal nevus, post-inflammatory hyperpigmentation (PIH), stasis dermatitis, and Riehl’s melanosis (see Ref. 7; other references^{8–17} included in Table 35.2). Multiple protocols have been described and studied in a variety of these pigmented lesions (Table 35.3).

Melasma

Melasma is an acquired disorder of hyperpigmentation appearing on sun-exposed areas that mostly involve the centrofacial region; histologically, one may see increased melanin, melanosomes, as well as melanocytes. Melasma is multifactorial, and pathogenesis may include genetic predisposition, pregnancy, cosmetics, medications, hormone therapies, phototoxic drugs, and ultraviolet radiation. Additionally, certain populations, such as African Americans, Asians, and Hispanics, have been noted to be particularly susceptible to melasma. Melasma can be classified histologically, with treatment implications, into three patterns based on the location of melanin deposition: epidermal, dermal, and mixed pattern.^{18–20} Epidermal melasma has been routinely treated with use of broad-spectrum sunscreens, chemical peels, bleaching agents such as hydroquinone, topical retinoids, lasers, as well as oral tranexamic acid (TNA).^{20–22} However, dermal and mixed-pattern melasma have remained particularly therapeutically challenging.²³ Overall, melasma is a chronic and relapsing condition that is particularly hard to treat in darker skin types (Fitzpatrick IV–VI) due to the increased risk of PIH. There is no universal efficacious treatment, and thus a combination approach is often undertaken.²² Over the past decade, IPL has emerged as a valuable technique in the treatment of melasma due to the efficacy and safety that it has demonstrated through extensive studies.

Table 35.1 Common definitions used in the description of IPL.

Incoherent	Waves are not in phase with one another in both time and space.
Polychromatic	Of multiple wavelengths.
Chromophores	Can be exogenous or endogenous; are light-absorbing chemicals, which absorb light of specific wavelength.
Pulse	The brief span of time for which the focused and scanned light beams interact with a given point on the skin, usually in milliseconds for IPL devices.
Fluence	Energy contained within light is expressed in Joules. The energy fluence determines the amount of energy delivered in a single pulse and is expressed in Joules/cm ² .
TRT ^{8,66}	It is the time taken for the target to dissipate about 50% of heat to surrounding tissues. It is related to the size of the target chromophore, e.g., a few nanoseconds (tattoo particles) to hundreds of milliseconds (leg venules).

Note: One of the primary differences between IPL and lasers is that lasers (which stands for light amplification by the stimulated emission of radiation) utilize monochromatic (light energy from a laser optical cavity of only a single wavelength), which is in direct contrast to the polychromatic nature of IPL.⁸

One of the first recorded uses of IPL in melasma was in 2001 by Moreno Arias et al.,⁶ who utilized IPL as a treatment for various melanocytic lesions, including five cases of melasma. Patients were treated for two and four sessions for epidermal and mixed melasma, respectively. In this study, the patients with epidermal melasma showed over 75% lightening, while those with mixed melasma showed poorer clearance with less than 25% lightening. Moreover, although no scarring, burns, or hypopigmentation was observed, PIH was recorded in patients with mixed melasma. This study demonstrated that IPL may be an effective therapy for the treatment of epidermal melasma, but should be cautiously used in mixed melasma due to the higher risk of PIH. Furthermore, this study demonstrated that long-term sun protection and bleaching creams should be utilized in patients with mixed melasma due to the increased risk of PIH.

A few years later, in 2004, Wang et al.²⁴ treated 17 Asian patients with IPL who were suffering from mixed melasma refractory to at least 3 months of 4% hydroquinone cream. All patients continued hydroquinone with sun protection while they were treated with four sessions of IPL. Immediately after treatment, there was a 39.8% improvement in relative melanin index (MI) compared to the 11.6% improvement in the control group. However, at 24 weeks follow-up, mean relative MI scores only demonstrated a 24.2% change from the original baseline, suggesting that maintenance treatments may be necessary. Moreover, there were two cases of transient PIH that resolved with

Table 35.2 Various disorders that may be treated with IPL, with level of evidence for IPL as a treatment, as determined by Wat et al.⁷

Vascular lesions	1. Telangiectasias^{1*} 2. Port-wine stains^{2*} 3. Rosacea^{2*} 4. Venous malformations^{3*} 5. Infantile hemangioma^{3*} 6. Erythrosis
Hyperpigmentation	1. Melasma^{1*} 2. Lentigines^{2*} 3. POC^{3*} 4. Ephelides 5. Riehl's melanosis 6. Stasis dermatitis pigmentation 7. PIH 8. Becker's nevus 9. Café au lait macule 10. Nevus spilus
Other	1. Acne vulgaris^{1*} 2. Sebaceous gland hyperplasia^{2*} 3. Actinic keratoses^{2*} 4. Hypertrophic scar^{3*} 5. Superficial basal cell carcinoma^{3*} 6. Bowen's disease^{3*} 7. Unwanted hair removal 8. Striae distensae 9. Skin rejuvenation

Sources: Babilas P et al., *Lasers Surg Med* 42(2) (2010):93–104; Bjerring P, Christiansen K, *J Cutan Laser Ther* 2(4) (2000):177–81; Chiu CS et al., *J Dermatolog Treat* 18(2) (2007):109–11; Raulin C et al., *Arch Dermatol* 135(6) (1999):679–83; Wenzel SM et al., *Dermatology* 217(3) (2008):286–90; Schroeter et al.; Papageorgiou P et al., *Br J Dermatol* 159(3) (2008):628–32; Ho WS et al., *Dermatol Surg* 30(6) (2004):887–90; discussion 890–1; Myers P et al., *J Cosmet Dermatol* 4(4) (2005):262–6; Jorge BF et al., *J Cosmet Laser Ther* 10(1) (2008):48–51; Sami NA et al., *J Drugs Dermatol* 7(7) (2008):627–32; Hernandez-Perez E et al., *Dermatol Surg* 28(12) (2002):1124–30; Moreno Arias GA, Ferrando J, *Dermatol Surg* 27(4) (2001):397–400; Kawada A et al., *Dermatol Surg* 28(6) (2002):504–8; Huang YL et al., *Dermatol Surg* 28(11) (2002):1007–12; discussion 1012; Wat H et al., *Dermatol Surg* 40(4) (2014):359–77.^{8–16}

Level 1 = 1*; level 2 = 2*; level 3 = 3*.

continued hydroquinone and IPL treatment. Otherwise, adverse effects in the study were minimal. In this study, Wang et al.²⁴ were able to demonstrate that IPL was a safe and effective treatment for refractory melasma in Asian individuals.

In 2008, a similar study was conducted by Li et al.²⁵ involving 89 patients with melasma refractory to various treatments including bleaching creams, chemical peels,

Table 35.3 Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds	Results
Moreno Arias et al. ⁶	Open label uncontrolled trial of 20 patients	Superficial lesions; café au lait macules (N = 4), epidermal melasma (N = 2), ephelides (N = 3), and lesions with deeper components; mixed melasma (N = 3), Becker nevus (N = 3), epidermal nevus (N = 2) and nevus spilus (N = 3)	II–IV	N/A	Differed for superficial and deep lesions, as follows 2 and 4 sessions at 4- and 8-week intervals; filters of 590 and 615; F of 34 and 38; double mode for each; PD of 3.8 and 4.5 with a delay of 20 and 20, respectively. Spot used varied according to the lesion size, but in general crystals of 8 mm, 8 mm and 45 mm, 10 mm were used.	>75% clearance for Café au lait macules, ephelides, and epidermal melasma; 51%–75% clearance for nevus spilus; <50% clearance for Becker's nevus, epidermal nevus, and mixed melasma. No repigmentation documented after average follow-up of 10.5 months.
Wang et al. ²⁴	Randomized control trial; 17 treatment, 16 controls	Mixed melasma refractory to treatment to at least 3 months of 4% hydroquinone cream	III–IV	Vasculight; ESC/ Sharplan, Yokneam, Israel	4 sessions at 4-week intervals; filter of 570 used in the first session and 590–615 filters used during subsequent sessions to treat residual deeper pigment. All sessions: F of 26–33; double pulse mode; PD of 3–4 and 4–5 with a delay of 30–35. All patients continued hydroquinone.	After treatment, there was 39.8% improvement in relative MI, compared to 11.6% improvement in the control group. At 24 weeks after treatment, mean relative MI scores only demonstrated a 24.2% change from original baseline.
Li et al. ²⁵	Open label uncontrolled evaluator-blinded trial of 89 patients	Melasma refractory to bleaching creams, chemical peels, or traditional Chinese medicine for at least 3 months	III–IV	Lumenis one; lumenis Co., Santa Clara, CA	4 treatments at 3-week intervals; protocol differed based on melasma type; epidermal type: filters of 560 to 590; double pulse. Mixed type: filters of 590 to 615 to 640; triple pulse. Both types: F of 13–17 (depending on the patients' skin type, melasma severity, and pain tolerability); PD of 3–4 with delay of 25–40.	At a 3-month follow-up: MI decreased from 140.8 -> 119.7 while erythema index (EI) decreased from 390.4 -> 201.9; mean MASI decreased from 15.2 -> 4.5; self-assessment indicated >50% improvement in 70.8% of patients; blinded physician assessment of >50% improvement in 77.5% of patients.

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Table 35.3 (Continued) Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds	Results
Zoccali et al. ²⁶	Open-label uncontrolled trial of 38 patients	Melasma	III–IV	Deka IPL device (Deka me.la. S.r.l., Calenzano-Florence, Italy)	Sessions ranged between 3 and 5 at intervals of 40–45 days; filter of 550; F of 6–14; PD of 5–10 with a delay of 10–20. Pretreatment skin care included 4 weeks of Kojic acid cream BID with alpha-hydroxy acid cream QAM.	All patients were followed up to 6 months with computer analysis showing ≥ 60% reduction in pigmented areas occurring in 76.3% of patients.
Goldman et al. ²⁷ ; *conflict of interest present	Prospective split-faced, randomized, evaluator-blinded, open-label study of 56 patients	Moderate (93%) to severe (7%) melasma	I–IV	N/A	2 IPL sessions at 4 weeks apart with sequential use of TTC cream for 2 weeks prior to first session till 4 weeks after last session. Filter of 560; F of 14–18; double pulse; PD of 3–3.5 and the delay time matched to skin type (10 for I, 20 for II, and 30 for III + IV). Side of face treated with TTC was randomized, with placebo on control side. TTC and placebo stopped 1 day before IPL treatments and resumed 1 day after.	Assessment occurred at 4 weeks after second IPL treatment (when TTC was stopped); both groups had significant improvement, although the group with IPL and TTC combined had greater improvement; clear or almost clear was seen in 57% of patients treated with combination therapy (IPL + TTC), while 23% of patients were classified as almost clear with IPL alone.
Figuiere et al. ²⁸	Prospective randomized, evaluator-blinded, open-label study; 31 in treatment group; 31 controls	Melasma refractory to TTC	II–V	Limelight, Cutera, Brisbane, CA, USA	Single session with a filter of 560; F from 12–22 based on skin phototypes. Other parameters not stated. TTC was started after the single session of IPL.	In IPL group: MASI from baseline showed 49.4% reduction (17.6 → 8.9) after 6 months and 44.9% reduction (9.7) after 12 months. Investigator's global assessment (IGA) showed at least moderate improvement in 67.8% of patients at 6 months and 64.5% at 12 months. In control group: no change in MASI; IGA showed at least moderate improvement in 15.8% at 6 months.

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Table 35.3 (Continued) Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds	Results
Na et al. ²⁹	Retrospective comparison study of 20 patients	Mixed-type melasma	III–IV	Ellipse Flex, Danish Dermatologic Development, Hoersholm, Denmark	Single session of IPL with 555–950 emission spectrum; F of 10–10.5; double pulse; PD of 2.5 and delay of 10; low fluence 1064-nm QS Nd:YAG laser was 2 weeks after the IPL session and performed four times with 1-week intervals.	One week after the last treatment modified-MASI (m-MASI) decreased by 59.35% on average; mean values of MI and EI decreased significantly (MI from 174 → 128; EI from 295 → 238).
Vachiramon et al. ³⁰	Prospective split-face, randomized study of 18 patients	Mixed-type melasma	Thai	IPL Device: Ellipse, Danish Dermatologic development, Hoersholm, Denmark; LF-QS-Nd:YAG laser: Revlite, Hoya Conbio, Fremont, CA	All patients received five sessions of full-face LF-QS-Nd:YAG laser at 1-week intervals; one side of face was randomized to also receive three IPL sessions immediately after LFQS at 2-week intervals; filters from 550 to 950; fluence of 6.8–8; double pulse; pulse duration of 2.5–3 with delay of 10; LFQS settings: 6-mm spot size, collimated homogenous flat-top beam profile, to deliver energy at 2.6–2.8 J/cm ² , 10 Hz for three passes. 2% hydroquinone was also used during study period.	Assessment occurred 12 weeks after last treatment; from baseline, modified-MASI (mMASI) decreased by 60% (14.85 → 6) on the combined side while 40% (15.8 → 9.5) decrease was seen in the LQFS group; relative lightness index (RLI) improved by 55% (8.05 → 3.66) on combined side and 37% (8.02 → 5.19) on LFQS only side.

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Table 35.3 (Continued) Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds	Results
Yun et al. ³¹	Prospective evaluator-blinded randomized comparison study of 24 patients; 12 treatment with 12 controls	Melasma	III–IV	IPL-F device: EcLatST; Union Medical, Seoul, Korea. LFQS-Nd:YAG laser: 1064-nm VRMIII; Lutronic, Seoul, Korea	Treatment group underwent six sessions of IPL-F (pulse-in-pulse IPL) with LFQS-Nd:YAG laser, while control had six sessions of IPL-F alone; intervals of 2 weeks were used. IPL-F settings included wavelength spectrum of 560–800; fluence of 13–15; 40-μs fractionated pulses; combination group received an additional 4 to 6 passes of LF-QS-Nd:YAG laser irradiation with a fluence ranging from 1.5 to 2.0 J/cm ² , a spot size of 6 mm, a pulse duration of 5 to 10 nanoseconds, and a frequency of 10 Hz on both cheeks. If there was a marked erythema or patients complained of pain or discomfort, authors waited 5 to 20 minutes before LF-QS-Nd:YAG application; otherwise, LF-QS-Nd:YAG was applied immediately after applying IPL-F to the entire treatment area.	At 2 months after treatment, the partial MASI scores in the combination group decreased significantly by 50% from baseline (12.75 → 6.50); in the IPL-F only group, the partial MASI score decreased 24% from baseline (12 → 9.17).
Cunha et al. ³²	Prospective study of 6 patients	Mixed type of melasma refractory to 4 month's treatment with Klingmans formula	III–IV	Harmonyxl of Alma Lasers (Israel) with hand-piece AFT (IPL); and Clearlift hand piece: LF-QS-Nd:YAG laser	Patient underwent three laser sessions with 1-month intervals; after each session, IPL was used; IPL settings included filter of 540 with F of 12–14 and "high pulse" of 12–15 milliseconds with undelayed delay. LFQS settings included: spot size of 5 mm, 1064 nm, pulse width of 20 nanoseconds, fluence 800–1000 mJ/P, pulse repetition rate 2 Hz. Between each session, all patients utilized a topic formulation with Klingman's formula (stopping application during 10 days after each session).	After the last treatment, MASI was significantly reduced by ~29% from baseline (8.0 → 5.7).

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Table 35.3 (Continued) Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds	Results
Chung et al. ³³	Prospective split-faced study of 12 patients	Melasma	N/A	Conventional IPL; Ellipse, Danish Dermatologic Development, Hørsholm, Denmark; LF-QS-Nd:YAG laser: Spectra, Lutronic Co., Seoul, Korea; F-IPL device: E-toning, Union Medical Co., Seoul, Korea	Half of the patient's face was treated with conventional IPL in addition to six sessions with LFQS every 2 weeks. A total of seven sessions occurred at 2-week intervals; the other half was treated with F-IPL. Conventional IPL parameters included F of 9–9.4; double pulse; PD of 2.5 and delay of 10; A LFQS Nd:YAG laser (8-mm collimated spot size, 10-nanoseconds pulse width, 1.0 to 1.2 J/cm ² of fluence, multiple passes to achieve mild transient erythema around melasma lesion) was used; F-IPL parameters: emitted 550–800 wavelength spectrum with fluence of 12–15 in 2–3 passes; PD of 40 μ s (fractionates a pulse duration of 10 milliseconds into 100 subpulses in which the pulse width of one subpulse is 40 μ s). From 2 weeks after the last treatment, they were instructed to apply topical hydroquinone 4% at night and topical antioxidant cream with a broad-spectrum sunscreen in the morning during the 6-month-follow-up period.	At 2 weeks follow-up, a significant decrease in MI was seen on both sides compared to baseline, but no statistical significant difference observed at 6 months; m-MASI decreased by 54.4% on the F-IPL side and by 50% on the IPL with LQFS side. Patients preferred F-IPL due to less discomfort during and after treatments.

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Table 35.3 (Continued) Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds	Results
Cho et al. ³⁴	Retrospective evaluator-blinded study of 51 patients	Melasma	III–IV	IPL: Ellipse Flex, Danish Dermatologic Development, Hoersholm, Denmark	Group A took oral TNA 500 mg/day while receiving IPL and three or four LFQS Nd:YAG laser treatments; group B: treated only with IPL and laser; IPL settings included wavelength emission of 555–950; F of 9.9–10.5; double pulses; PD of 2.5 and delay of 10; 2–3 week intervals occurred, and then patients returned for LFQS treatment using the following parameters: a spot size of 8 mm, and fluences from 1.0 to 1.2 J/cm ² , 10 Hz; mean 6–8 passes; 1–2 week intervals were between laser treatments.	At 2 weeks' after the last treatment: the oral TNA and IPL group experienced decreases in mMASI from 11.33 at baseline to 6.21, while the IPL and laser group only experienced mMASI decrease from 11.7 → 8.93; patient's self-assessment of melasma improvement was higher in the TNA/IPL group.
Bjerring and Christiansen ³⁵	Open-label uncontrolled trial of 26 patients	Lentigo solaris (N = 18) and benign melanocytic nevi (N = 8)	I–III	Ellipse Flex; Danish Dermatologic Development, Hoersholm, Denmark; LFQS 1064-nm Nd:YAG laser (Spectra, Lutronic, Korea)	A single treatment with wavelength range of 400–720; F of 10–20 (10 to 14 for lentigines, 14 to 20 for nevi); double pulse; PD of 7 with delay of 25; only one lesion was treated in each patient.	At 2 months' follow-up, 96% of patients had pigment reduction, and the average clearance was 74.2% for lentigo solaris and 66.3% for melanocytic nevi.
Kawada et al. ³⁶	Open-label uncontrolled trial of 60 patients	Facial pigmented lesions: solar lentigines (N = 45), ephelides (N = 7), solar lentigines + ephelides (N = 8)	I–III	Natulight, Lumenis, Tokyo	Average of four sessions at intervals of 2 to 3 weeks; filter of 560; F of 20–24 (fluence increased by 1 at subsequent treatment according to previous session results); double or triple pulses; PD of 2.6–5.0 with delay of 20	Evaluation occurred 2–4 weeks after final treatment; in solar lentigines group: 40% had over 50% improvement while 16% had more than 75% improvement, large plaques responded more poorly; in the ephelides group: 71% had >50% improvement; in the solar lentigines + ephelides group: 75% had >50% improvement.

(Continued)

Table 35.3 (Continued) Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds	Results
Huang et al. ³⁷	Prospective study of 36 patients	Facial ephelides	III–IV	Vasculight (ESC/ Sharpplan, Yokneam, Israel)	Average of 1.47 sessions with intervals of 4 weeks; filters of 550 to 590; F of 25–35; single or double pulse; PD of 4 with delay of 20–40. Duration for procedure ranged from 10 to 15 minutes.	6 months' follow-up; Freckles area and severity index (FASI) improved by 58%; a mean of 1.45 sessions was needed to achieve >50% clearance in 86.1% of patients; 91.7% of patients were extremely or very satisfied.
Sasaya et al. ³⁸	Open-label uncontrolled trial of 31 patients	Solar lentigines of hands	Japanese	Lumenis One, LUMENIS, Koutou-ku, Tokyo	Three to five sessions at 4- to 5-week intervals; filter of 515; F of 10 to 12; single or double pulse; PD of 4 with delay of 20.	Physician assessment demonstrated >50% improvement in 62% of the patients and >75% improvement in 23% of patients.
Wang et al. ³⁹	Prospective randomized evaluator-blinded split-faced study of 32 patients	Ephelides (N = 15) or lentigines (N = 17)	III–IV	Quantum SR (ESC Medical Systems Ltd, Yokneam, Israel); QSAL used: AlexLAZR, Candela Laser Corp, Wayland, Mass	One session of QSAL and two sessions of IPL at 4-week interval; wavelength emission range of 560 to 1200; F of 26–30 for session 1 and 28–32 for session 2; double mode; PD of 3.2–6.0 at intervals of 40; QSAL parameters: 755 nm, 50 nanoseconds, 3-mm spot size, fluence of 6.5–7.5 J/cm ² .	Evaluated at 12 weeks from initial session with pigmentation area and severity index score (PSI); Freckles achieved greater improvement after QSAL (85.5% decrease in PSI) than IPL (79.8% decrease); in lentigines, similar reduction in PSI was achieved between IPL and QSAL (~62%), although IPL was superior in terms of fewer occurrences of PIH, 0% for IPL and 28% for QSAL.

(Continued)

Table 35.3 (Continued) Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds	Results
Park et al. ⁴⁰	Retrospective case series of 25 patients	Complex dyspigmentation (defined as >2 types of facial pigimentary disorders including ephelides, solar lentigines, and melasma, among others)	III–IV	IPL device N/A; QSRL device: model Lambda Photometrics, Hertfordshire, England	IPL sessions varied by lesion with mean of 2.88 for entire cohort with intervals of 3 to 4 weeks; filter of 560 (superficial lesions) or 590 (deeper lesions); F of 20–25; double pulse mode with PD of 2.4–4.0/4.0–5.0 with a delay of 15; QSRL at low fluence was added during the same session or within 1 week of the IPL treatment to target pigmented lesions that remained. QSRL parameters include mean 1.52 sessions with 694 nm with spot size of 3–4 mm, fluence of 4.5–6 J/cm ² , and pulse durations of 25 nanoseconds. TTC was also used throughout the study.	Mean follow-up of 1 month after completion of treatment; two physician evaluations determined that 60% of patients achieved >75% clearing; mean IPL sessions needed for patients with lentigines was 2.95 with a mean result of >50% clearing.
Galeckas et al. ⁴¹ ; *conflict of interest present	Prospective randomized split-faced evaluator-blinded study of 10 patients	Facial dyschromia (Lentigines, erythema, telangiectasias)	I–III	Starlux, Palomar Medical Technologies, Burlington, MA; 595-nm PDL used; Perfecta, Candela, Wayland, MA	Three treatments were given at 3- to 4-week intervals; filter used N/A; fluence of 32–40; PD of 10–20; pulses were delivered at 0.5 Hz with no overlap (all final IPL treatments had fluence of 36 with PD of 10); PDL parameters include first pass: 10-mm compression hand piece with fluence of 6.5 to 8.0 J/cm ² with a pulse duration of 1.5 milliseconds. Parameters differed for second pass used (10-mm spot with fluence of 9.5 to 10, 20-millisecond duration with cryogen spray cooling enabled (30–40 millisecond spray with 20-millisecond delay) with pulses delivered at 1.5 Hz with ~15% overlap.	One month follow-up; for PDL and IPL, respectively, blinded physicians reported 86.5% versus 82.0% improvement of dark lentigines, and 65.0% versus 62.5% improvement of light lentigines.

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Table 35.3 (Continued) Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds	Results
Kontoets et al. ⁴²	Case report	Lentigines in LEOPARD syndrome	III	Photoderm VL/PL (ESC Scharplan, Yokneam, Israel)	Various sessions depending on body area ranging from one to five with a minimum interval of 4 weeks; parameters used varied by body area and session number; 570 or 590 nm; F range from 25–40; double to triple pulse; PD of 2.5–3.0 with a delay of 20–30.	All of the lentigines that were treated responded to therapy; some were completely removed while the rest faded to a varying extent. Results maintained at 2-year follow-up.
Remington et al. ⁴³	Case report	10-year-old female with facial lentigines in Peutz–Jeghers syndrome	Caucasian	N/A	Series of 12 treatments to each different facial region was required because of pain tolerance (most regions required one treatment only) with 4– to 8-week intervals; filter of 590; F of 47; triple pulse; PD of 3.2 with delay of 20.	Most lentigines resolved after a single treatment with a few areas requiring a second treatment; drastic improvement was noted.
Raulin et al. ⁴⁴ , 1997	Prospective study of one patient	POC	N/A	PhotoDerm VL (ESC Ltd., Yokneam, Israel and Needham, MA)	Ten sessions at unknown intervals; filter of 550; F 21.5–31; single pulse; and PD of 3–5 with unrecorded delay.	100% clearing.
Weiss et al. ⁴⁵ ; *conflict of interest present	Retrospective study; chart review of 135 patients	POC	N/A	Undeclared device by ESC/Sharplan, Needham, Mass.	Varying sessions with mean of 2.78 at intervals of 4 weeks; filter of 515; F of 20–24 (increased by 1–3 when < 50% improvement observed from previous session); single or double pulse; PD of 2–4 with delay of 10; Some final treatments consisted of a double pulse using 550 or 570 filter (to target deeper and larger telangiectases).	82% of patients experienced >75% improvement after typically three treatments.

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Table 35.3 (Continued) Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds	Results
Goldman et al.²⁷; *conflict of interest present	Retrospective study; chart review of 66 patients	POC	N/A	Undeclared device by ESC/Sharplan, Needham, Mass.	As-needed sessions at intervals of 4 weeks; varying parameters but most started with filter of 515; F of 30–34 (increased by 5–10% when < 50% improvement observed from previous session); double pulse; PD of 2–4 with delay of 10; final treatments typically consisted of a double pulse using 550 or 570 (to target deeper and larger telangiectases)	Follow-up 1 month after treatment; >75% improvement in telangiectasias and hyperpigmentation was seen in 42% of patients after a mean of 2.8 treatments.
Rusciani et al.⁴⁵	Prospective study of 175 patients	POC	I–III	Vasculight Plus, ESC/Sharplan, Yokneam, Israel	Three sessions at 3-week intervals; filter of 550 in first session with F of 32–36; double or triple pulse, PD of 2.5–3.5 with delay of 10–20. Subsequent sessions had filters of 515 and 590 (for superficial and deep lesions, respectively) in addition to fluence of 33–38; double and triple pulse mode; PD of 2.5–4.5 and delay of 10–30.	At 3 months' follow-up, 95% had >50% reduction in poikilodermal lesions; 81% had >75% improvement; 85% of patients were very satisfied; Best results were obtained with 550- and 590-nm filters with fluence of 32–36 J/cm ² in double pulse of 3–4 milliseconds with a delay of 10 milliseconds.
Gold et al.⁴⁶	Case report	Nevus spilus	Caucasian	N/A	Four sessions at unknown intervals; filter of 590; F varied by session as follows (40, 39.9–46, 39.9–46, 20–24); triple pulse mode in first three sessions and double pulse for last treatment; PD varied by session (3, 3.5, 3.5, 2.5) with a delay of 20.	6-month follow-up with marked clearing.
Pimentel et al.⁴⁷	Case report	Stasis dermatitis of bilateral legs	Caucasian	Harmony system, Alma Lasers Ltd., Caesarea, Israel	Three sessions with undeclared intervals; filter of 570; F of 10–12; undeclared pulse mode; PD of 15 with undeclared delay.	Restoration of normal skin color with no repigmentation at 6-month follow-up; initially the lesions darkened but then lightened thereafter.

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Table 35.3 (Continued) Various IPL protocols.

Study	Type of study	Disorder	Skin type or ethnicity	IPL and/or laser used	IPL laser protocol: Session(s) and interval(s), cut-off filter(s) and/or wavelength range in nm, fluence(s) (F) in J/cm ² , pulse mode(s), pulse duration(s) (PD) in milliseconds, and delay(s) in milliseconds			Results
Li et al. ⁴⁸	Case series of six patients; randomized split-faced evaluator-blinded treatment	Riehl's melanosis	IV	Lumenis One, Lumenis Co., Santa Clara, CA	Variable with up to 10 sessions with undeclared intervals; serial usage of 590, 640, and 695 filters; F from 11–17; triple pulse; PD of 3–4 with delay of 35–40.			At 6-month follow-up, all patients experienced at least a "good" (five-point global improvement assessment) outcome with significantly decreased MI and EI on IPL treated side versus control side. An average of 80% decrease in hypermelanosis was demonstrated, without recurrence during the 8-month follow-up.
Paque et al. ⁴⁹	Case series of two patients	Facial hypermelanosis/PIH secondary to trimethoprim-sulfamethoxazole induced toxic epidermal necrolysis	II	Multilight, ESC Medical Systems Ltd, Yokneam, Israel	Five sessions at 4- to 6-week intervals; filters of 550, 590, and 615; F of 25–32; double to triple pulse mode; PD of 2.2–3.2 with a delay of 30. To treat superficial pigmentation treatments started with a shorter cut-off filter, 550, with F of 25 and single pulse mode with PD of 3.6. For deeper pigmentation, the cut-off filter was raised along with the F and pulse mode.			
Ho et al. ⁵⁰	Open label uncontrolled trial of 19 patients	Post-burn hyperpigmentation w/o grafts	III–IV	Multilight™ (ESC Medical Systems Ltd, Yokneam, Israel)	Three to seven sessions with intervals of 3–4 weeks; filters of 550, 570, and 590 (sequentially increased if no improvement seen in the last session in order to target deeper pigmentation); F of 28–46; double pulse mode; PD of 1.7–4 with delay of 15–40; treatments were started by using the 550 cutoff filter at a F of 28, PD of 1.7, and a delay of 15 to treat superficial pigmentation. F and PD were increased gradually until endpoint of erythema or slight increase in darkness of hyperpigmentation was observed.			Follow-up from up to 32 months with no recurrence of hyperpigmentation; ~79% of patients had >50% clinical clearance. One patient had complete (100%) clearing; 20.8% of patients had <50% improvement.

or traditional Chinese medicine. Treatment protocol involved four IPL treatments. At 3 months follow-up, a blinded dermatologist determined that 77.5% of patients experienced over 50% improvement with a significant decrease in pigmentation. Additionally, mean melasma area and severity index (MASI) scores decreased considerably from 15.2 to 4.5 after treatment. Similar to the study by Wang et al., Li et al.²⁵ demonstrated that IPL was particularly effective in the treatment of refractory melasma. Further studies over the years continued to demonstrate the effectiveness of IPL in the treatment of melasma. In 2009, Zoccali et al.²⁶ used IPL in 38 patients with melasma. Sessions ranged from three to five, and all patients were followed up to 6 months. An impressive 76.3% of patients saw over 60% reduction in hyperpigmented areas.

While IPL has been used alone as a treatment for melasma, several studies have demonstrated a successful combination treatment of IPL with other therapies, such as triple therapy cream (TTC; composed of fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%). In 2011, Goldman et al.²⁷ conducted a 10-week split-faced, evaluator-blinded, and randomized study in which 56 patients with moderate to severe melasma were treated with IPL for two sessions and TTC. At baseline, in both groups, 93% of patients were classified as moderate and 7% were severe. One month after the last session, when TTC was stopped, a subjective improvement of clear or almost clear was seen in 57% of patients treated with combination therapy, while 23% of patients treated with IPL and inactive cream were noted to be almost clear.²⁷ The efficacy of this combination treatment was reinforced in a randomized evaluator-blinded open-label study by Figueiredo et al.²⁸ in 2012 where a single session of IPL followed by TTC was used to treat 31 patients with melasma refractory to TTC, while a control group received TTC with broad-spectrum sunscreens. The IPL with TTC group had a reduction in MASI scores by 49% from baseline at 6 months and 44.9% reduction at 12 months, versus no change in the control group. Three cases of transient PIH occurred in patients with skin type IV that resolved with bleaching agents within 4 to 6 months.²⁸ These two studies demonstrated that IPL, while effective alone in the treatment of melasma, may have improved efficacy when combined with therapies such as TTC. Moreover, in recent years, IPL has also been demonstrated to be effective as a combination therapy with low-fluence Q-switched (LFQS) Nd:YAG laser as well as with oral TNA.^{29,30,32,34} Lastly, recently a new type of IPL has been developed that provides 40-microsecond fractionated pulses and has been demonstrated, in at least two separate studies, to be an effective and safe treatment modality for melasma, although more studies are warranted.^{31,33}

From the current literature, we can conclude that IPL may be a reasonable therapeutic option in the treatment of melasma, particularly when refractory to prior treatments.⁵¹ Furthermore, IPL when combined with TTC, oral TNA, or LFQS laser may result in an added level of efficacy than IPL alone. Additionally, it has been observed that the

benefits seen with IPL may require continued maintenance treatments and thus should be discussed with the patient when deciding on treatments. Furthermore, many different IPL devices, including the recent development of new fractionated IPL devices, as well as protocols, exist for the treatment of melasma (Table 35.3) and should be carefully considered when planning treatments. Lastly, the use of proper sun protection before and after treatments should be strongly encouraged.

Lentigines and ephelides

Lentigines and ephelides are commonly observed lesions by physicians. Lentigines tend to occur after adolescence and vary in size and color. These lesions increase in quantity with age and may be unevenly distributed on the body. Histological analysis of a lentigo will show epidermal and melanocytic hyperplasia. Interestingly, while Caucasians tend to experience rhytides with photoaging, Asian individuals are more prone to developing lentigines. Conversely, ephelides occur in early adolescence and are fairly uniform in color and size. Additionally, ephelides exhibit epidermal hypermelanosis upon histological analysis.^{52–54} Given the high prevalence of both of these lesions, IPL has become a widely researched therapeutic option.

In 2000, Bjerring and Christiansen³⁵ evaluated the effectiveness of IPL in the treatment of lentigo solaris in 18 patients. A single treatment of IPL was given and then evaluated at 2 months, where an average clearance of 74.2% was observed. In this study, Bjerring and Christiansen³⁵ concluded that IPL was found to be both safe and effective for removal of benign pigmented lesions such as lentigines. In 2002, Kawada et al.³⁶ evaluated 60 Asian patients with solar lentigines and ephelides; at a 2–4 week follow-up, more than 50% improvement was observed in 48% of the patients following three to five IPL treatments. Although there was a disproportionate sample size between the two conditions, in this study, ephelides responded better than lentigines and small-plaque lentigines responded better than large-plaque lentigines. Furthermore, there were no reports of PIH in any of the participants.³⁶ In the same year, Huang et al.³⁷ used IPL to treat ephelides in 36 Asian patients; a mean of 1.45 sessions was needed to achieve over 50% clearance at 6 months follow-up in 86.1% of the patients. Nearly 10 years later, Sasaya et al.³⁸ completed a study on 31 patients with solar lentigines of the hands who received three to five IPL treatments. In this study, they noted over 50% improvement in 62% of the patients without any adverse effects noted.³¹

Several studies have also evaluated the efficacy of IPL versus lasers in the treatment of lentigines and ephelides. One of the first studies to evaluate this was that in 2006 by Wang et al.³⁹; Wang et al. conducted a randomized physician blinded split-faced study in which IPL was compared with Q-switched alexandrite laser (QSAL)⁵⁵ as a treatment for Taiwanese women with ephelides ($n = 15$) or with lentigines ($n = 17$). Protocol involved one session of QSAL and two sessions of IPL and follow-up at 12 weeks from initial session. In the ephelides group, pigmentation

area and severity index (PSI) scores improved by 79.8% versus 85.5% for IPL and QSAL, respectively. In the lentigines group, similar improvements were seen with the use of both modalities with no statistically significant difference, ~62% improvement from baseline. However, adverse events from treatment were not equal between these groups; in patients with lentigines, the incidence of PIH was significantly higher with QSAL, 28%, when compared to IPL, 0%. In this study, Wang et al.³⁹ demonstrated that, for ephelides, QSAL was slightly superior to IPL in terms of number of treatments and end results, while both modalities produced similar results in the treatment of lentigines, although IPL offered reduced risk for PIH and thus may be preferred. Furthermore, they hypothesized that for ephelides, more than three sessions of IPL might be required to obtain the same efficacy as one session of QSAL therapy.³⁹

Soon after, in 2008, Park et al.⁴⁰ investigated the combination use of IPL with Q-switched ruby laser (QSRL) as a treatment for complex dyspigmentation (a phenomenon that includes ephelides, solar lentigines, and melasma, among others). The majority of patients had lentigines while a few also had ephelides. Overall, patients were treated with IPL on an as-needed basis, while QSRL at low fluence was added during the same session or within 1 week of IPL treatment. Patients also utilized TTC in between therapies in order to minimize PIH. With a mean follow-up of 1 month after completion of treatment, two independent physicians judged that 60% of the patients had over 75% improvement. The mean IPL sessions needed for patients with lentigines was 2.95 with a mean result of greater than 50% clearing. Side effects from this study were transient PIH in three patients and linear hypopigmentation in one patient. This study concluded that combination treatment of IPL and QSRL may be an effective and safe treatment for pigmentations such as ephelides and solar lentigines among Asian patients.⁴⁰

In the same year as the study by Park et al.,⁴⁰ Galeckas et al.⁴¹ conducted a randomized split-faced evaluator-blinded comparison of IPL and pulsed dye laser (PDL) on 10 patients with facial dyschromia (lentigines, erythema, and telangiectasias). Three treatments were given and assessed at 1 month follow-up. For PDL and IPL, respectively, blinded physicians reported 86.5% versus 82.0% improvement of dark lentigines and 65.0% versus 62.5% improvement of light lentigines. Interestingly, in patients treated with PDL, 50% experienced infraorbital edema and 10% experienced post-treatment purpura; these adverse effects were not observed in the IPL group.⁴¹

While lentigines tend to have benign associations, they may also be present in syndromes such as LEOPARD syndrome and Peutz-Jeghers syndrome (PJS). In one case study by Kontoes et al.⁴², a female suffering from LEOPARD syndrome was treated with IPL with varying sessions depending on the body area. All of the lentigines that were treated responded to therapy; some were completely removed, while the rest faded to a varying extent. Of particular mention is that these results were maintained

at a 2-year follow-up.⁴² Similar success was demonstrated by Remington et al.⁴³ in the treatment of a patient with PJS who had multiple facial lentigines successfully treated with IPL.

In conclusion, IPL is an effective and safe therapy for the treatment of ephelides as well as lentigines, particularly in the Asian population where the risk of PIH is increased with QSRL. It is important to note that IPL also has demonstrated relatively less side effects when compared to PDL in the treatment of lentigines. When deciding between lasers or IPL in the treatment of lentigines, one should consider reviewing the advantages and disadvantages of IPL and lasers with the patient; if cost effectiveness is a concern, one can perform laser test areas to determine if the outcome is satisfactory. If adequate, these patients can undergo treatment with lasers and, usually, experience satisfactory results in one to two sessions. However, if PIH develops at test sites, then IPL should instead be considered.⁵⁶

Poikiloderma of Civatte

POC is a specific variant of poikiloderma that refers to a combination of atrophy, telangiectasia, and reddish-brown pigment changes. Many treatments of POC such as electrosurgery, cryotherapy, argon lasers, KTP lasers, and PDL lasers have been unsatisfactory both in terms of effectiveness and side effects that may include scarring and further dyspigmentation.^{57–59} This has left many patients suffering from POC with relatively few viable treatment options. As a response to the scarcity of treatment options, IPL has been researched as a possible therapy for patients with POC.

The use of IPL in the treatment of POC has been researched in over 300 patients across multiple studies. The earliest effectiveness of IPL in the treatment of POC was observed in a study by Raulin et al.⁴¹ in 1997 where one patient treated for POC experienced 100% clearing in 10 sessions with IPL. Years later, in 2000, Goldman and Weiss demonstrated similar efficacy with IPL in two retrospective studies; together they reviewed 201 patients with POC who were treated with IPL. In one review of 66 patients, over 75% improvement in hyperpigmentation and telangiectasias was seen in 42% of patients after a mean of 2.8 treatments. In the other review of 135 patients, 82% of patients had over 75% reduction of poikiloderma changes, after typically three treatments. Between both reviews, a few cases of transient mild purpura were observed that resolved without sequelae in 3 to 5 days, which is quicker than that observed in purpura induced by laser treatment, which can take 1 to 2 weeks. It is important to note that only a few participants experienced small areas of hypopigmentation, two of which persisted at a 2-year follow-up. Nonetheless, Goldman and Weiss demonstrated that IPL was effective in treating both the hyperpigmented and telangiectatic components of POC.^{4,23}

In 2008, Rusciani et al.⁴⁵ also evaluated the use of IPL as a treatment for POC in 175 patients. At 3 months follow-up, after three treatments at 3-week intervals, an

astounding 95% had greater than 50% reduction in poikiloderma lesions; even more impressive was that 81% saw over 75% improvement. Adverse effects were minimal and included transient mild purpura in 18%. Moreover, few patients with darker skin types had transient blisters that resolved in 7 days without dyspigmentation or scarring.⁴⁵

In conclusion, although numerous high-quality randomized studies have yet to be conducted, IPL has been demonstrated to be a safe and efficacious treatment modality for POC, a disorder with otherwise unsatisfactory alternative treatments. It should be noted that while mild purpura appears to be a somewhat frequent adverse effect of IPL therapy, it is transient and resolves quicker than that which may be induced by laser therapy.⁶⁰ Moreover, before considering treatment with IPL, one must take into consideration that POC is a disorder of both vessels and pigmentation, and thus selective photothermolysis of hemoglobin and melanin must be achieved for successful treatment.

Melanocytic lesions and others

IPL has been further studied as a therapy for other pigmented lesions such as nevus spilus, café au lait macule, Becker's and epidermal nevus, PIH, stasis dermatitis, and Riehl's melanosis.

A nevus spilus is usually acquired in early childhood and appears, most commonly on the trunk or extremity, as a tan or lentiginous lesion where many dark nevus-like lesions may emerge resulting in a spotted appearance; development of melanoma in these lesions is a rare but reported event.⁶¹ There have been a few reported studies of the use of IPL in the treatment of this relatively uncommon lesion; in 1999, Gold et al.⁴⁶ reported a case where a patient with a nevus spilus experienced marked clearing after four sessions of IPL; this result was maintained for a 6-month follow-up.

In addition to nevus spilus, other various melanocytic lesions have been observed as being treated with IPL. In 2001, Moreno Arias et al.,⁶ through using IPL, observed over 75% clearance in patients with café au lait macules, ephelides, and epidermal melasma. However, nevus spilus only showed a clearance of 51%–75%, while Becker's nevus, epidermal nevus, and mixed melasma showed less than 50% clearance. Interestingly, repigmentation was not documented after an average follow-up of 10.5 months. Of note is that protocols differed depending on the depth of the lesion, and only a small sample of patients with each disorder was studied.⁶ Additionally, 1 year prior, Bjerring and Christiansen³⁵ evaluated the use of IPL in treating eight patients with benign melanocytic nevi. A single treatment of IPL was given and then evaluated at 2 months. Patients experienced an average clearance of 66.3% in their lesions.³⁵

Stasis dermatitis has also been reported in literature as being treated with IPL; in a case report by Pimentel et al.,⁴⁷ one patient with stasis dermatitis secondary to chronic venous insufficiency was successfully treated with IPL. In this study, the normal skin color was restored without repigmentation at 6 months follow-up. It should be noted that initially the lesions darkened but then lightened thereafter.⁴⁷

IPL has also been studied as a treatment for an unusual pigmented condition known as Riehl's melanosis, which presents as a brown or bluish reticulate pigmentation on the face and neck. In a small case series of six patients by Li et al.,⁴⁸ all patients experienced at least a "good" outcome with decreased melanin and erythema index.

PIH is relatively common and can present as an adverse reaction from certain drug eruptions; in one study by Paquet et al.,⁴⁹ two men with severe hypermelanosis of the face due to sulfonamide-induced toxic epidermal necrolysis were treated with IPL for five sessions, and an average of 80% decrease in hypermelanosis was demonstrated, without recurrence during the 8-month follow-up. Similar efficacy of IPL has also been demonstrated in the treatment of post-burn hyperpigmentation.^{50,62}

ADVANTAGES AND DISADVANTAGES OF IPL

IPL devices are quite versatile and economical as they can treat various conditions, have a relatively lower purchase price when compared to lasers, and have a high skin coverage rate. Other advantages include a relatively easy application, minimal preoperative preparation, no downtime, and limited post-treatment care.^{1,40} Furthermore, when compared to lasers in the treatment of pigmented disorders, particularly when used in dark-skinned individuals, IPL has been associated with fewer side effects such as pigmentation changes.^{36,39,41}

Some disadvantages to IPL may include the need for multiple treatments to observe similar outcomes as those seen with QSAL,³⁹ the need for maintenance treatments,²⁴ and that deeper lesions may be unresponsive to treatment.⁶ Other disadvantages include inconsistency from pulse to pulse of emitted spectrum and fluence,⁶³ large spot size, inability to focus light, weight of the hand piece, and the requirement of direct contact with a hand piece and gel application—both of which prohibit observation of an immediate local response.¹

CLINICAL CONSIDERATIONS BEFORE TREATMENT WITH IPL

Before beginning treatment with IPL, a clinician should assess whether or not the patient has responded to more cost-effective and/or better studied therapies, such as lasers or topicals, for the condition of interest. This decision should factor in the relative lower risk of PIH compared to lasers and lack of downtime with IPL, balanced with the possibility of multiple treatments and maintenance therapy. Furthermore, before introducing IPL, its risks and benefits should be discussed. Lastly, a proper IPL protocol should be decided upon by the physician, taking into account the multiple properties of IPL and how they may be adjusted for treatment of the lesion of interest as well as the skin type being treated.⁸

Multiple preparations should take place prior to initiation of IPL treatment. For example, in order to help reduce the risk of PIH, sun protective and bleaching agents should be preferably used 3 months prior to treatment, although 6 weeks may be sufficient.⁶⁴ The patient's skin

type should also be determined by using the Fitzpatrick⁶⁵ scale, as treatment parameters may need to be adjusted. Additionally, photodocumentation should be performed prior to each single treatment.⁶⁶ The area to be treated should be shaved and free of any topical cosmetic preparations such as makeup; an optical coupling gel needs to be applied to the targeted area. Suitable eye protection using appropriate goggles should also be used during treatment.¹ If the area to be treated is located near the eyes, then eyelids should remain closed to avoid phototoxic damage to eye tissues such as the retina.⁶⁷ Moreover, it has been suggested that if a melanocytic lesion that is not desired to be treated is located within the treatment area, one should cover the lesion with wet white gauze or nonabsorbent white paper.¹

When a treatment protocol is first being utilized in an individual, a test treatment should be conducted on a spot area located in a discreet site to observe the skin reaction, which may be evaluated 6 weeks later. Furthermore, since sebaceous glands and skin thickness vary by region, the incidence of side effects also varies by region, thus requiring sample treatments based on different parameters and regions. While minor pain or burning has been seen in a majority of patients during or immediately after treatment, this should be transient and the patient should be asked about any other reactions. If the utilized treatment protocol produces no significant adverse effects in the test area, then one can proceed to test the desired treatment area. When treating areas, each spot should overlap the previous one by 10%.¹ Additionally, when treating a well-defined smaller lesion, a perforated plastic shield with varying aperture sizes may be helpful; matching an aperture to the lesion to be treated may allow precise application of light.⁶⁸

In 2015, Adamic et al.⁶⁶ released guidelines of care for vascular lasers and intense pulse light sources, although with a primary focus on treatment of vascular lesions; some of these guidelines for post-treatment care include cooling the treated area and UV protection, as well as avoidance.¹⁵ A following session may be considered 4 to 6 weeks later.¹

ADVERSE EFFECTS AND SAFETY OF IPL

The adverse effects and safety profile of IPL have been evaluated across multiple studies. IPL almost always results in swelling and erythema, which may last for a few days; using a low fluence may minimize erythema. Blistering and crusting are also common but may be a sign of high fluence treatment; if present, patients must strictly avoid scratching, which may result in infections and scar formation—moreover, utilizing antimicrobial ointments may help avoid superinfections by bacteria.¹

Additionally, IPL is almost always associated with minor pain during treatment; cooling during or after IPL treatment and/or the addition of topical anesthesia can produce relief in most patients.¹ Moreover, epidermal cooling can protect the epidermis from thermal injury⁶⁶; cooling may be in the form of a chilled, colorless gel used

during the procedure or with new devices that integrate continuous contact cooling.^{25,66}

Other potential side effects include dyspigmentation, atrophy, scarring, and infection. Scarring occurs rarely and almost always with excessive fluence and/or from manipulation of crusting.¹⁵ Additionally, proper precautions can minimize the risk of PIH including sun avoidance and protection,⁶⁶ compression of skin surface during treatment,⁶⁴ as well as proper spot testing.¹

Several types of patients should be treated cautiously with IPL including those suffering from long-term diabetes, those suffering from coagulopathies, patients with implants in the treatment area, or patients with a heart pacemaker. Lastly, patients with a history of herpes simplex require an antiviral prophylaxis for facial treatments.^{1,15,43,66} Multiple patients should be excluded from IPL therapy, including patients that are pregnant, are breastfeeding, are using retinoids or photosensitizing medications, have a suntan, or are suffering from photosensitive diseases.^{1,69}

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